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Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.01/A1

Topic: A.02. Postnatal Neurogenesis

Support: JPB Foundation

Title: Effects of motor learning on subventricular zone neurogenesis in adult mice

Authors: *B. ZHOU[1,2], M. HEIMAN[2,3];
[1]Picower Inst. of Learning and Memory, Massachusetts Inst. of Technol. (MIT), Cambridge, MA; [2]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Picower Inst. of Learning and Memory, Cambridge, MA

Abstract: In adult rodents, spatial learning increases neurogenesis in the hippocampal dentate gyrus. Similar effects have not previously been shown for the other major neurogenic niche in the rodent brain, the subventricular zone (SVZ). Although most SVZ-born neurons travel to the olfactory bulb, a small fraction instead migrate laterally into the striatum. Given the striatum's role in motor learning, we asked if motor learning increases adult SVZ neurogenesis. To test this hypothesis, adult male C57Bl/6 mice were trained on the rotarod task and injected with 5-ethynyl-2'-deoxyuridine (EdU) to label dividing cells. Two control groups were used: mock training mice that sat stationary atop an unmoving rotarod, and naive mice that remained in their home cage. Brains were collected 1, 7, and 30 days after the task and immunohistochemically processed with EdU, doublecortin (DCX), and NeuN for quantitative analysis of neuronal proliferation and survival at various timepoints. FACS sorting of EdU-labeled nuclei was used as a secondary measure. We found that motor learning increases SVZ neurogenesis, with a 1.4-fold increase in EdU+ cells and a 1.8-fold increase in total EdU intensity in rotarod mice over mock training mice one day after the task. Importantly, a set of control experiments using a treadmill instead of rotarod showed no difference in SVZ EdU labeling between running and stationary mice, excluding exercise as a confounding factor. DCX expression in the SVZ was initially elevated 1.7-fold in both rotarod and mock training mice but returned to baseline in mock training mice 7 days later, while remaining high in rotarod-trained mice. These results suggest that learning-induced neurogenesis continued in the week after motor training. The effects of the rotarod task were also visible in the striatum over extended periods. Striatal EdU+ cells were more abundant in rotarod trained mice both 7 and 30 days after training. In addition, migrating EdU+ / DCX+ neurons were present in the striatum at 7 days after training, and though rare, surviving striatal EdU+ / NeuN+ neurons were identified at 30 days after training. Overall, these results demonstrate the neurogenic impact of motor learning in the adult rodent SVZ and suggest that motor learning may drive migration of immature neurons into the striatum.

Disclosures: B. Zhou: None. **M. Heiman:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.02/A2

Topic: A.02. Postnatal Neurogenesis

Support: SIMR
NIH R01DC016696

Title: Differentiation of Perinatal Olfactory Sensory Neurons from Neural Crest-Derived Cells

Authors: *A. FANG[1], M. TREESE[1], C. R. YU[1,2];
[1]Stowers Inst. for Med. Res., Kansas City, MO; [2]Dept. of Anat. and Cell Biol., Univ. of Kansas Med. Ctr., Kansas City, MO

Abstract: The olfactory epithelium in mice comprises cells differentiated from both olfactory placodes and neural crest cells. Most olfactory sensory neurons (OSNs) are thought to originate from the olfactory placodes, but recent studies suggest that neural crest cells also differentiate into OSNs. The navigator cells, which are perinatally born OSNs, play an important role in setting up the olfactory map and guiding later-born OSNs to project to their target glomeruli in the olfactory bulbs (OBs). We hypothesize that neural crest cells, which exhibit high migratory and axon dynamics, could differentiate into the navigator cells. By injecting 4-OH tamoxifen into the Sox10-CreER;Ai14 mice at precise time points, we found neural crest cells labelled around E8.5 could differentiate into OSNs. Moreover, these neural crest cells derived OSNs disappeared after P10, which is consistent with the disappearance of the navigator cells postnatally. Through lineage tracing of tdTomato$^+$ cells, we found these tdTomato$^+$ progenitors migrated through the lamina propria to populate the OE after E16.5. Moreover, the tdTomato$^+$ progenitors became quiescent horizontal basal cells (HBCs) after P0. These neural crest cells generated HBCs function as normal HBCs to repopulate the entire OE after ablation. These results indicate that neural crest cells supply two important populations of cells in the OE, the perinatal navigator cells that are essential for establishing the olfactory map, and the quiescent stem cell population responsible for repopulating the OE after extensive injuries.

Disclosures: A. Fang: None. **M. Treese:** None. **C.R. Yu:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.03/A3

Topic: A.02. Postnatal Neurogenesis

Support: BICAN U01

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

Authors: *Y. GAO[1], C. V. VELTHOVEN[2], C. LEE[3], E. THOMAS[1], N. DEE[2], J. GOLDY[2], K. SMITH[2], B. TASIC[3], Z. YAO[2], H. ZENG[3];
[1]Allen Inst., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: The mammalian brain is highly heterogeneous and develops through a series of temporally regulated events that are crucial for its proper function. The mechanisms underlying the development of different cell types and their spatial organization are not fully understood. Single-cell RNA-sequencing offers a unique opportunity to study cell types across the entire temporal range of brain development. In this study, we present a dataset of single-cell transcriptomes obtained from the prenatal (E11.5 to E18.5) and postnatal (P0 to P56) stages of the mouse visual cortex (VIS). The dataset includes 86,595 prenatal and 377,727 postnatal cells collected from VIS and processed by single-cell RNA sequencing on the 10x Genomics v3 platform. We developed a computational approach to construct the cell type lineage based on the transcriptomics data, enabling us to explore the critical differentiation events and birth dates of different cell types. Furthermore, we have explored the temporal dynamics of transcriptomes at the cluster and subclass levels and identified genes associated with lineage bifurcations or other developmental events. To validate our findings, we compared the expression patterns of selected genes with the Allen ISH Developing Mouse Brain Atlas. Collectively, our analysis reveals cell-type specific changes during brain development and provides the most detailed transcriptomic examination of brain development in the cortex.

Disclosures: Y. Gao: None. **C.V. Velthoven:** None. **C. Lee:** None. **E. Thomas:** None. **N. Dee:** None. **J. Goldy:** None. **K. Smith:** None. **B. Tasic:** None. **Z. Yao:** None. **H. Zeng:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.04/A4

Topic: A.02. Postnatal Neurogenesis

Support: NIH BICAN Grant U01MH130962

Title: Multi-omic Single-Cell Profiling of the Developing Mouse Brain

Authors: *E. THOMAS, Y. GAO, C. LEE, K. SMITH, J. GOLDY, A. CHAKKA, A. TORKELSON, T. PHAM, R. FERRER, J. GUZMAN, M. BENDER, K. JAMES, J. RODGRIGUEZ, N. DEE, T. CASPER, W. HO, M. CLARK, J. GLOE, R. MCCUE, M.

READING, E. LIANG, K. RONELLENFITCH, V. WRIGHT, C. PAGAN, L. NG, M. KUNST, C. VAN VELTHOVEN, Z. YAO, B. TASIC, H. ZENG;
Allen Inst., Seattle, WA

Abstract: The mouse brain is a highly complex and heterogeneous structure consisting of thousands of diverse cell types. A comprehensive understanding of the brain's development is critical for understanding the origins and specifications of these diverse cell types. To this end, we outline a plan to molecularly profile the whole mouse brain over the course of development at single-cell resolution. Here, we present the beginning of these efforts, showcasing single-cell multi-omic data at P0 and other early postnatal timepoints. At each of these timepoints, ten regions of interest (cerebellum, cerebral nuclei, cortical subplate, hindbrain, hippocampal formation, hypothalamus, isocortex, midbrain, olfactory area, and thalamus) were profiled with both 10x Genomics' single-cell RNA-seq v3.1 and Multiome (simultaneous single-nucleus RNA-seq and ATAC-seq) platforms. Following integration and clustering of these datasets, we utilized differences in gene expression and chromatin accessibility to define, at various taxonomical levels, the cell types present at these developmental stages. These data will serve as an important foundation in building a comprehensive, single-cell atlas of the developing mouse brain.

Disclosures: E. Thomas: None. **Y. Gao:** None. **C. Lee:** None. **K. Smith:** None. **J. Goldy:** None. **A. Chakka:** None. **A. Torkelson:** None. **T. Pham:** None. **R. Ferrer:** None. **J. Guzman:** None. **M. Bender:** None. **K. James:** None. **J. Rodgriguez:** None. **N. Dee:** None. **T. Casper:** None. **W. Ho:** None. **M. Clark:** None. **J. Gloe:** None. **R. McCue:** None. **M. Reding:** None. **E. Liang:** None. **K. Ronellenfitch:** None. **V. Wright:** None. **C. Pagan:** None. **L. Ng:** None. **M. Kunst:** None. **C. van Velthoven:** None. **Z. Yao:** None. **B. Tasic:** None. **H. Zeng:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.05/A5

Topic: A.02. Postnatal Neurogenesis

Support: the Study (Group) of the Health Effects of Heavy Metals Organized by the Ministry of the Environment
Grants-in-Aid for KAKENHI from MEXT [22K11403]

Title: Neurodegeneration & Subsequent Recovery: Exploring Neurogenesis in the Dorsal Root Ganglion of Methylmercury-Exposed Rats

Authors: *Y. SHINODA[1], Y. SEKIGUCHI[1], A. MATSUKI[1], E. YOSHIDA[2], T. TAKAHASHI[1], T. KAJI[3], Y. FUJIWARA[1];
[1]Tokyo Univ. of Pharm. and Life Sci., Hachioji, Tokyo, Japan; [2]CRIEPI, Abiko, Chiba, Japan; [3]Tokyo Univ. of Sci., Noda, Chiba, Japan

Abstract: Methylmercury (MeHg) is known to cause severe neural degeneration in the central and peripheral nervous systems, resulting in a condition known as Minamata disease. Our recent findings demonstrated selective hypoalgesia in MeHg-exposed rats, which exhibited time-dependent recovery. Concurrently, we observed a decrease in the number of neurons in the dorsal root ganglion (DRG) of MeHg-exposed rats during hypoalgesia, followed by restoration to control levels upon behavioral recovery. In this study, we conducted immunohistochemistry to investigate the occurrence of neurogenesis over time in MeHg-exposed DRGs. Wistar rats were orally administered MeHg (6.7 mg/kg/day) for 5 days, with a 2-day discontinuation period, followed by another cycle. Additionally, BrdU (100 mg/kg/day) was intraperitoneally administered for 5 days, starting a week before fixation. Rats were fixed with paraformaldehyde, and their DRGs were cryosectioned and processed for immunohistochemistry between seven and 70 days after MeHg exposure initiation. The sections were immunostained with Ki67 and BrdU antibodies as neuronal and nuclear markers. Our results revealed the presence of Ki67-positive matured neurons during the recovery phase, while BrdU-positive neurons were not detected. These findings are intriguing as Ki67-positive cells typically indicate non-resting phase (G0) cells, whereas matured neurons are generally in a resting phase. We aim to further investigate this phenomenon and provide an explanation during the upcoming conference.

Disclosures: **Y. Shinoda:** None. **Y. Sekiguchi:** None. **A. Matsuki:** None. **E. Yoshida:** None. **T. Takahashi:** None. **T. Kaji:** None. **Y. Fujiwara:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.06/A6

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant MH125367
NIH Grant MH128745
Valencian Council PROMETEO/2019/075
Spanish Ministry PCI2018-093062

Title: Delayed maturation and migration of excitatory neurons in the juvenile mouse paralaminar amygdala

Authors: P. ALDERMAN[1], D. SAXON[2], L. TORRIJOS-SAIZ[3], M. SHARIEF[1], C. PAGE[1], S. BIAGIOTTI[1], V. BUTYRKIN[4], A. MELAMED[1], C. T. KUO[5], S. VICINI[6], J. GARCIA-VERDUGO[3], V. HERRANZ-PEREZ[3], J. CORBIN[7], ***S. SORRELLS**[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [3]Univ. of Valencia, Valencia, Spain; [4]Univ. of Maryland, Col. Park Neurosci. and Cognitive Sci. Program, Washington, MD; [5]Dept. of Cell Biol., Duke Univ. Sch. of Med., Durham, NC; [6]Dept Parmacology & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [7]Ctr. for Neurosci. Res., Children's Natl. Hlth. Syst., Washington, DC

Abstract: The human amygdala contains a large population of immature excitatory neurons in the paralaminar nucleus (PL) that develop along a delayed timeline from birth to adulthood. It is not known if a similar population of neurons are present in the mouse amygdala. We identified the homologous region corresponding to the mouse paralaminar amygdala containing immature excitatory neurons which has previously been considered part of the amygdala intercalated cell clusters or ventral endopiriform cortex (vEN). These immature neurons are born embryonically, not from postnatal neurogenesis, and a subpopulation of them migrate into nearby regions during juvenile ages. These immature neurons begin to exhibit molecular and physiological maturation during juvenile ages (P21-P28). The finding of a similar region with immature neurons in both humans and mice suggests a potentially conserved cellular mechanism for neuron maturation and migration during adolescence, a key time period for amygdala circuit maturation and related behavioral changes.

Disclosures: P. Alderman: None. **D. Saxon:** None. **L. Torrijos-Saiz:** None. **M. Sharief:** None. **C. Page:** None. **S. Biagiotti:** None. **V. Butyrkin:** None. **A. Melamed:** None. **C.T. Kuo:** None. **S. Vicini:** None. **J. Garcia-Verdugo:** None. **V. Herranz-Perez:** None. **J. Corbin:** None. **S. Sorrells:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.07/A7

Topic: A.02. Postnatal Neurogenesis

Support: UNAM-PAPIIT-IG200121
CONAHCYT CF-2023-G-243

Title: New vista of postnatal neurogenesis and cell migration in hypothalamic vasopressinergic nuclei of the rat

Authors: *M. A. ZETTER, L. ZHANG;
Physiol., Natl. Autonomous Univ. of Mexico, Mexico City, Mexico

Abstract: In early 1990s, Dick Swaab and collaborators reported that hypothalamic vasopressin and oxytocin nuclei (VON) of the pig change in size and cell number during various postnatal developmental stages and in response to changes in gonadal-reproductive status. They suggested that the VON neurons undergo postnatal neurogenesis according to physiological demands. However, these observations went largely unnoticed. By analyzing numerous sets of whole rat brain serial sections with immunohistochemistry against vasopressin (AVP-ir), we observed quite a few morphological features that suggested the AVP-ir neurons could disperse from the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei postnatally. The lateral hypothalamus was observed as the main target region, but they were also found in other subcortical regions, always adjacent to AVP-ir fibers that formed bundles and/or matrices. These

tunnel-like structures outlined by AVP-ir fibres contained AVP-ir cell bodies. Derived from these observations, we hypothesized that PVN and SON must undergo postnatal neurogenesis to replenish the nuclei. We devised a simple experiment by repeated administration of 5-bromo-deoxyuridine (BrdU) for 15 days in control rats and with water deprivation (24 hr/48hr). BrdU-ir nuclei were present in PVN and SON, and this phenomenon was increased in the experimental group. The BrdU-ir nuclei were large and round shaped and frequently paired, as twin-BrdU-ir nuclei. By double-labeled immunofluorescence AVP/BrdU, we corroborated that some BrdU-ir cells were indeed becoming AVP-ir mature neurons. These findings are consistent with the early studies (*vide supra)* and provide new insights into the current controversy on adult neurogenesis in the mammalian hypothalamus.

Disclosures: M.A. Zetter: None. **L. Zhang:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.08/A8

Topic: A.02. Postnatal Neurogenesis

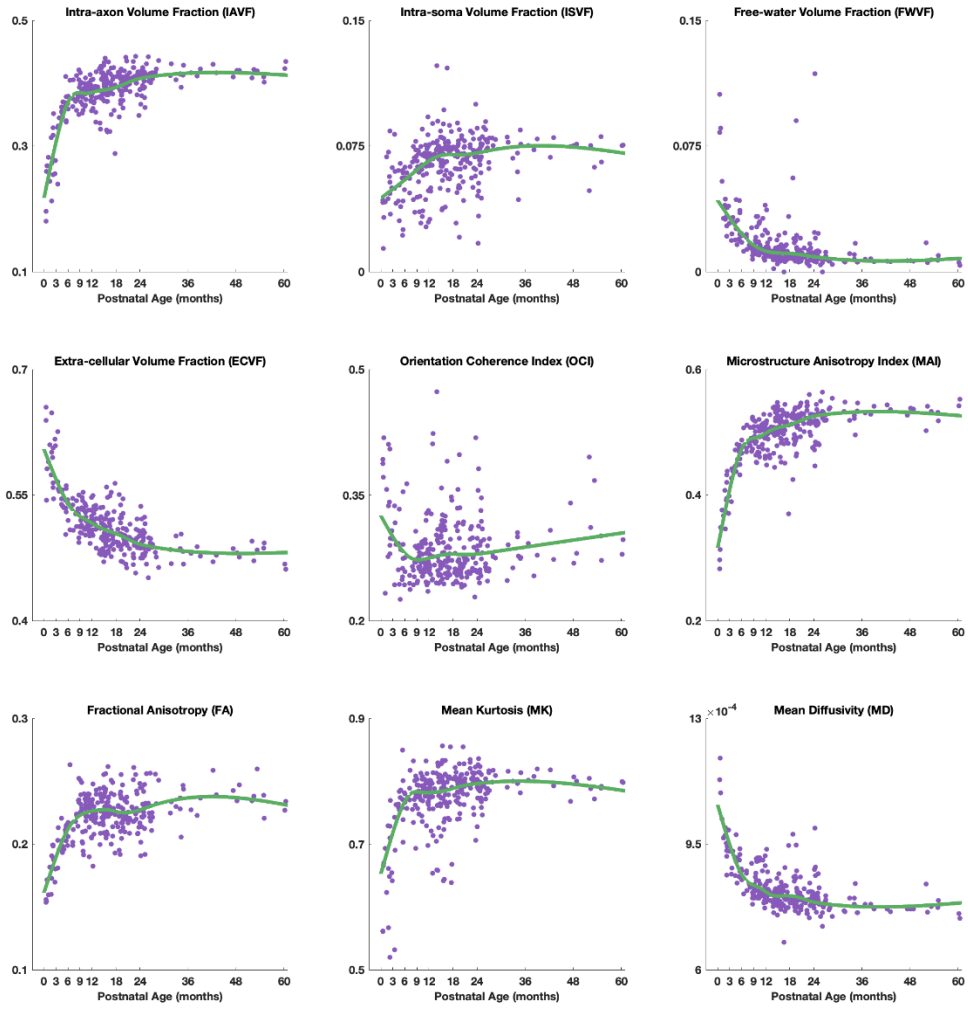
Support: MH125479
EB008374

Title: Early Postnatal Development of Tissue Microstructure in the Human Cerebellum

Authors: *K. HUYNH, S. AHMAD, P.-T. YAP;
Dept. of Radiology, Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: While the cerebellum plays an important role in multiple human brain functions, the development of its tissue micro-architecture during the first years of life is not fully understood. Here, we charted cerebellar microstructural changes between birth and 5 years of age using over 280 structural and diffusion MRI datasets acquired from 174 children. Deep learning was used to isolate the cerebellum using T1w and T2w images. Microstructure measurements including diffusion anisotropy, tissue volume fraction, orientation coherence, and diffusivity were then calculated based on microstructure fingerprinting and diffusion kurtosis. Developmental trajectories were charted as a function of age, subject, and gender using generalized additive mixed models. We found increases in intra-axonal (IAVF) and intra-soma (ISVF) volume fractions, kurtosis, and anisotropy; and decreases in extracellular and free-water volume fractions, and diffusivity. These trends indicate growth in axons and somas (increase in IAVF and ISVF), and increase in cellular complexity (increase in kurtosis), progression in myelination (increase in anisotropy), and reduction of water content (decrease in free-water and extracellular volume fractions). Axonal growth is particularly rapid during the first 6 months, evidenced by sharp increases in IAVF and anisotropy. Soma growth takes place at a slower pace and peaks only at the 15th month. Interestingly, fiber orientation coherence index (OCI) decreases until the

6th month and increases thereafter. This trend is corroborated by the increasing and then slightly decreasing trend of the mean kurtosis. Most developments stabilize at 2 years of age.



Disclosures: **K. Huynh:** None. **S. Ahmad:** None. **P. Yap:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.09/A9

Topic: A.02. Postnatal Neurogenesis

Support: grant 2018SHZDZX05
grant No. 2021ZD0203200-03

Title: Single-cell transcriptome profile of the medial preoptic area during development

Authors: *Z. YU[1,2,3], X. XU[1,3];
[1]Inst. of Neurosci., Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China; [3]Shanghai Ctr. for Brain Sci. and Brain-Inspired Intelligence Technol., Shanghai, China

Abstract: The medial preoptic area (mPOA) of hypothalamus is known to be sexually dimorphic and regulates sex-specific social behaviors in adult. Yet, the developmental processes that regulate sexual differentiation of the mPOA remains unclear. We hypothesize that sexually dimorphic functions of the mPOA may emerge from critical transcriptional changes that occur during specific developmental windows. We fluorescently labelled the mPOA using a genetic intersectional strategy, specifically by crossing three different transgenic alleles. Such fluorescent labelling facilitates micro-dissection of the mPOA during different developmental stage. Subsequently, single-cell RNA sequencing was performed for the mPOA dissected from postnatal day 1(P1), postnatal day 21 (P21) male and female mice respectively. We have transcriptionally profiled ~12998 cells from the mPOA of P1 mice and ~26365 cells from P21 mice to date. We found that the expression of some genes showed significantly difference between the two sexes in a developmental stage dependent manner. The relative proportion that each cell type cluster makes up was also sexually dimorphic and changed along with the development. Our study reveals for the first time developmentally modulated sex differences in cell type composition in the mouse mPOA, which could lead to further insight into the molecular mechanisms that underlie sex specific mPOA functions in adulthood.

Disclosures: Z. Yu: None. **X. Xu:** None.

Poster

PSTR059. Temporal and Spatial Patterning of Neurogenesis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.10/A10

Topic: A.02. Postnatal Neurogenesis

Support: Michael Smith BC's Health Research Trainee Fellowship
BC Children's Hospital Mining for Miracles Postdoctoral Fellowship
BCCHRI: Brain, Behaviour and Development Theme

Title: Investigating the Role of Novel MicroRNAs in Granule Cell Development during Mouse Cerebellar Development

Authors: *M. RAHIMI-BALAEI, M. RAMIREZ, D. GOLDOWITZ;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Gene mutations and/or environmental perturbations during cerebellar development can alter the pattern of gene expression via deregulation of epigenetic factors and result in cerebellar dysfunction and a wide range of neurodevelopmental disorders. MicroRNAs (miRNAs) are key regulators of gene expression. The role of miRNAs in the development of various epochs of postnatal (P) granule cell development [proliferation (P0), post mitotic/differentiation (P3), migration (P6), and maturation/synaptogenesis (P9)] was assessed by isolating cerebellar granule cells at these timepoints and extracting m- and mi-RNAs. After m/miRNA-sequencing, a bioinformatic exploration of the transcriptional data was completed to create a catalog of miRNAs and mRNAs in granule cells at different developmental stages (1978 distinct miRNAs and 18000 mRNAs were detected). The focus was on miRNAs that were expressed in a dynamic pattern over the four timepoints (875 with a $P<0.05$ over the 4 time points). Not surprisingly, the most significant changes over time was between P0 and P9; with 57 down and 39 upregulated miRNAs ($P<0.05$ and log2foldchange≥ 2). The miRWalk tool was used to predict microRNA binding sites which enabled filtering for 3'UTR targets and binding *p*-values > 0.95. In the next step, the negative correlation (-0.8 - -1) of these filtered miRNAs with potential mRNA targets was explored using m/miRNA seq reads (35 downregulated and 17 upregulated miRNAs met criterion). The candidate miRNAs that have already reported targets in Google Scholar were selected (10 miRNAs). The candidate miRNA, miR-382-5p and its mRNA target, Nfia [a member of the NF1 (nuclear factor 1) family of transcription factors], emerged with the stringent negative correlation (-1). To validate miR-382-5p as a viable candidate for further study: 1) The miRNA and its target were quantitatively replicated with RT-qPCR demonstrating that miR-382-5p expression was downregulated while Nfia expression was upregulated ($P<0.0001$); 2) Expression was spatially validated with *in situ* hybridization (mRNAscope and miRNAscope HD Assay Red) showing miR-382-5p and Nfia mRNA highly expressed in GCs and also detected in astrocytes, and 3) miRNA targeting sites were examined using a Luciferase reporter gene assay and confirmed the interaction between miR-382-5p and Nfia mRNA. Currently, we are establishing experimental conditions to both knockdown and over-express miR-382-5p, *in vitro* and *in vivo*, to understand its role in cerebellar granule cell development. The deliverables will be an atlas of miRNAs during granule cell development and the demonstration of the role of miR-382-5p in granule cell development.

Disclosures: M. Rahimi-Balaei: None. **M. Ramirez:** None. **D. Goldowitz:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.01/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NINDS R01 NS111220

Title: A developmental cell atlas of the mouse brain by mass cytometry

Authors: A. L. VAN DEUSEN[1], A. KEELER[1], C. DEPPMANN[1], ***E. R. ZUNDER**[2];
[1]Univ. of Virginia, Univ. of Virginia, Charlottesville, VA; [2]Biomed. Engin., Univ. of Virgina, Charlottesville, VA

Abstract: Development of the mammalian brain requires precisely controlled differentiation of neurons, glia, and nonneural cells. To investigate protein-level changes in these diverse cell types and their progenitors, we performed single-cell mass cytometry on whole brain (E11.5/E12.5) and microdissected cortex, diencephalon, midbrain, and hindbrain (E13.5-P4) from C57BL/6 mice. These samples were collected and analyzed with biological replicates for every day of development across all microdissected tissues, for 112 sample replicates in total. After pre-processing and clean-up gating, we quantified 24,290,787 cells with a 40-antibody panel optimized for mouse brain development. Global clustering across all timepoints and tissues identified 85 molecularly distinct cell populations, quantified across embryonic and postnatal development. Differentiation trajectory analysis was used to identify the sequential molecular transitions from immature NSC/RGCs to mature neuronal and glial cell types. We also observed dynamic changes in what appear to be cell engulfment events by microglia, indicating that this mass cytometry approach may be useful to monitor how phagocytosis regulates nervous system development. Comparison to published scRNA-seq measurements revealed considerable discrepancies between protein and mRNA abundances in the developing brain, demonstrating the value of protein-level measurements for identifying functional biomolecules and cell states. Overall, our findings demonstrate the utility of mass cytometry as a high-throughput, scalable platform for single-cell profiling of brain tissue.

Disclosures: A.L. Van Deusen: None. **A. Keeler:** None. **C. Deppmann:** None. **E.R. Zunder:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.02/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF Grant 2020R1A6A3A03038387

Title: Mirine is a novel microprotein required during neurogenesis

Authors: *Y. KIM[1], B. S. NILGES[2], N. POGODALLA[2], N. KRUSY[3], A. BOUTSEN[3], E. RAZ[4], L. NGUYEN[3], S. A. LEIDEL[1];
[1]Univ. of Bern, Bern, Switzerland; [2]Max Planck Inst. for Mol. Biomedicine, Münster, Germany; [3]GIGA-Stem Cells, Univ. of Liège, Liège, Belgium; [4]Inst. of Cell Biol., Univ. of Münster, Münster, Germany

Abstract: The brain contains the most extensive pool of long-noncoding RNAs (lncRNAs) compared to other organs. A significant portion of these lncRNAs have remained

uncharacterized and are believed to function solely as conventional lncRNA. However, the unexpected discovery of short open-reading-frame-encoded peptides (SEPs) has put a new perspective on such lncRNA molecules. This emerging field in biology focuses on the discovery and characterization of novel, previously unannotated or misannotated SEPs with the promise to unveil uncharted territory. SEPs, previously overlooked due to their small size and often low expression levels, have been identified in numerous organisms including insects, plants, and vertebrates. These microproteins have revealed unexpected roles in development, cell polarity, metabolism, and signaling.
Recently, new high-throughput methods such as ribosome profiling and quantitative mass spectrometry have facilitated the identification of previously unknown microproteins. Given that the brain expresses the largest number of noncoding RNAs among all organs, it is expected to harbor a wealth of novel microproteins. Therefore, we performed a translatome and proteome analysis of zebrafish and mouse brain to identify functional SEPs. We identified 198 and 121 novel small open reading frame (smORF) candidates in zebrafish and mouse brain, respectively. Among the identified candidates, we focused our analysis on MIRINE, an 83 amino acid microprotein. MIRINE is conserved between vertebrates and contains a transmembrane domain, which led MIRINE localized on plasma membrane and transport vesicles in cells. Interestingly, MIRINE exhibits increasing expression levels at neurogenesis stages during brain development, in particular in cortical and hippocampal neurons, while being absent in early-stage progenitor cells or non-neuronal cells. Downregulation of MIRINE resulted in increased cell proliferation and reduced maturation of Neuro2A cells, suggesting its requirement in neurite maturation during neurogenesis Finally, we determined the interactome of MIRINE and identified several proteins required for protein transport in neurons including synaptic vesicle proteins, shedding light on the potential mechanistic pathway of MIRINE during neurogenesis.

Disclosures: **Y. Kim:** None. **B.S. Nilges:** None. **N. Pogodalla:** None. **N. Krusy:** None. **A. Boutsen:** None. **E. Raz:** None. **L. Nguyen:** None. **S.A. Leidel:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.03/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI Grant 16K20902 to T.K.
JSPS KAKENHI Grant 18K14999 to T.K.

Title: The function of N-Kinesin family motor protein in cytokinesis in neural stem cells during cortical development

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Abstract: During development, the mammalian cerebral cortex undergoes a complex series of sequential processes that involve the proliferation of neural stem cells (NSC) and the differentiation and migration of neurons. The NSCs are located in the ventricular/subventricular zone of the cortex and self-renew to expand the progenitor pool and subsequently produce neurons. In cell line studies, the N-Kinesin family motor protein participates in central spindle organization, midbody formation, and cytokinesis. Mutations in the human *N-KINESIN* gene have been linked to microcephaly in humans. However, molecular and cellular processes that are impacted by the mutated *N-Kinesin* and the mechanisms of its action during normal cortical development are not fully understood. Here, we found that this Kinesin was highly expressed in the NSCs of the developing cortex and localized in midbodies during mitotic cell division. To investigate the function of the N-Kinesin during early brain development, we used *in-utero* electroporation to deliver siRNA with an EGFP expression vector. Knockdown of *that N-Kinesin* increased apoptotic cell death by upregulating DNA damage and p53, and induced early cell cycle exit by triggering the p53/p21 pathway. A subset of cells failed to complete the cytokinesis, which led to binucleated cells. We observed that depletion of the Kinesin also impaired mitotic spindle assembly and orientation, resulting in abnormalities in the NSC division. Our findings suggest that the N-Kinesin is crucial for regulating NSC survival and cytokinesis during brain development, and its impairment may lead to cortical malformations.

Disclosures: **S. Naher:** None. **T. Kikkawa:** None. **N. Osumi:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.04/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI Grant Numbers JP20K07237
Takeda Science Foundation

Title: Transport of CyclinD2 mRNA in radial glial cells regulates their cell cycle progression and subsequent corticogenesis

Authors: ***T. KIKKAWA**[1], Y. WAKAMATSU[1], Y. U. INOUE[2], T. INOUE[2], N. OSUMI[1];
[1]Dept. of Developmental Neurosci., Tohoku Univ. Grad. Sch. of Med., Sendai, Miyagi, Japan;
[2]Dept. of Biochem. and Cell. Biol., Natl. Inst. of Neurosci., Kodaira, Tokyo, Japan

Abstract: Radial glial (RG) cells are the stem/progenitor cells in the developing cortex, characterized by their apico-basally polarized and elongated basal processes. Our previous research in mice has demonstrated that mRNAs of *CyclinD2* (*Ccnd2*), a gene coding a cell cycle regulator, are transported to the basal end-foot of the RG cell. We have also identified that its 3′UTR is sufficient for this basal transport as a “zip code” (*cis*-acting transport element, CTE; Tsunekawa et al., EMBO J, 2012). To investigate the functional importance of the CTE, we

employed CRISPR/Cas9 system to delete the CTE in mice. In this mutant cortex, *Ccnd2* mRNA failed to localize in the basal end-feet, and instead accumulated in the RG cell soma. These findings unequivocally establish the essential role of the CTE in mediating the basal transport of *Ccnd2* mRNA. While the *Ccnd2* mRNAs has been shown to be locally translated in the basal end-feet of the RG cells, it remained unclear if Ccnd2 proteins in the basal end-foot would be transported to their nucleus. By employing a combination of photo-conversion and time-lapse imaging, we successfully visualized a basal-to-apical translocation of the photo-converted exogenous Ccnd2 proteins along the basal processes of the RG cells. This compelling evidence suggests an active transport mechanism of the Ccnd2 proteins from the basal end-foot to the nucleus, thereby modulating the cell cycle progression. Our investigations also revealed that the CTE-deleted cortex exhibited a shortened cell cycle in the RG cells. Considering that the length of the basal processes increases with the growth of the cortex, we propose that the transport of the *Ccnd2* mRNA and protein along the basal process may contribute to the lengthening of the cell cycle. Consequently, this cell cycle defect likely underlies the observed decrease of the cortex thickness in the CTE-deleted mice.

Disclosures: **T. Kikkawa:** None. **Y. Wakamatsu:** None. **Y. U. Inoue:** None. **T. Inoue:** None. **N. Osumi:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

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Program #/Poster #: PSTR060.05/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: AMED Grant JP21wm0425003
JSPS KAKENHI JP30884217
JST SPRING Grant JPMJSP2114
JSPS Grant 23KJ0193

Title: Unraveling the molecular mechanisms underlying sex differences in the mammalian corticogenesis: insights from a Pax6 mutant mouse model of neurodevelopmental disorder

Authors: *S. MANABE, S. OCHI, N. OSUMI;
Dept. of Developmental Neurosci., Tohoku University, Grad. Sch. of Med., Sendai, Miyagi, Japan

Abstract: Neurodevelopmental disorders, including autism spectrum disorder (ASD), exhibit a gender difference in prevalence and pathology. Traditionally, exposure to the sex hormones during the perinatal period has been considered to be the primary trigger for sexual differentiation of the brain (*Phoenix et al., 1959*). However, emerging evidence suggests that gene expression patterns in the rodent cortex differ between sexes even during the embryonic period (*Wolstenholme et al., 2013; Pradhan et al., 2021*), raising the possibility that sexual

differentiation is predetermined in the embryonic cortex. Nevertheless, the molecular mechanisms governing sexual differentiation of the cortex prior to the perinatal period remain incompletely understood. To shed light on the molecular mechanism underlying sexual differentiation of the cortex during the embryonic period, we employed *Pax6* mutant mice, as previous studies have shown notable sex differences in both cortical morphology and vocal communication in *Pax6* mutant rats (*Umeda et al., 2010; Hiraoka et al., 2016*). Using bulk RNA-seq analysis, we investigated the embryonic cortex derived from male and female wild-type (WT), *Pax6* mutant heterozygote, and homozygote mice at embryonic day 14.5. Our findings, as shown in both UMAP clustering analysis and the number of differentially expressed genes (DEGs), revealed that *Pax6* mutant heterozygote mice exhibited the most prominent sex difference in gene expression levels compared to WT and homozygote counterparts. Furthermore, we identified *Dusp11*, a gene involved in regulation of the cell proliferation, as a significant DEG between *Pax6* mutant heterozygote males and females. Intriguingly, we also observed a sex difference in the neural progenitor cell population within these groups. Notably, several DEGs were found to be regulated by the estrogen receptor (ERα), suggesting a potential involvement of the sex hormones prior to the perinatal period in sexual differentiation of the cortex. In summary, our results suggest that molecular pathways influenced by sex hormones may play a crucial role in shaping the cell dynamics of the developing cortex during the embryonic period. By elucidating the molecular mechanism underlying gender differences in the prevalence and pathology of the ASD, our research contributes to a deeper understanding of neurodevelopmental disorders.

Disclosures: **S. Manabe:** None. **S. Ochi:** None. **N. Osumi:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.06/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI JP30884217
AMED JP21wm0425003

Title: Automated analysis of rodent behavior using IntelliProfiller: a potential tool for studying neurodevelopmental disorder-like model mice

Authors: *S. OCHI[1], H. INADA[2], N. OSUMI[1];
[1]Tohoku Univ., Sendai, Japan; [2]Natl. Ctr. Neurol. Psychiat., Kodaira, Japan

Abstract: Autism spectrum disorder (ASD) is prevalent neurodevelopmental disorder (NDD) characterized by deficits in social communication and repetitive behaviors. With an increase number of children being diagnosed with ASD, there is a growing need to understand mechanisms and symptoms of NDDs to develop effective treatments and interventions. Animal

models have been instrumental in studying NDDs, employing classical behavioral paradigms such as the open field test and the social interaction test. However, consistency in results can be challenging due to human involvement. To address this issue, we have developed a novel system, IntelliProfiler, which enables automated analysis of rodent behavior. IntelliProfiller allows us to analyze the relative distances between individual mice and the travel distances of multiple mice, each embedded with a transponder, without image analysis. The system provides a unique opportunity to evaluate the relative social distance between individuals and groups, which can serve as an indicator of affinity to others or anxiety in a social environment. Our preliminary analysis using IntelliProfiler revealed pronounced differences in social interaction between littermates of wild-type (WT) and a mouse model of ASD (*Pax6* heterozygous mutant; $Pax6^{Sey/+}$). Notably, these differences the three-chamber test, in our previous study (Yoshizaki et al., 2016). Additionally, $Pax6^{Sey/+}$ female mice exhibited hyperactive behavior and sleep disturbance, suggesting a potentially comorbidity with attention deficit hyperactivity disorder (ADHD). These findings are further supported by our previous research involving $Pax6^{rSey2/+}$ female rats, which exhibited reduced vocal communication and decreased brain volume (Umeda et al., 2010; Hiraoka et al., 2016). Collectively, our data suggest that $Pax6^{Sey/+}$ female mice may serve as a valuable model for studying severe ASD-like features, potentiall with concomitant ADHD. The application of IntelliProfiller in studying neuropsychiatric behaviors in NDD model mice holds significant promise, offering several advantages over classical behavior analyses. These advantages include 1) the ability to conduct a long-term studies of basal activity in a non-contact setting and 2) quantitative analyses of anxiety in social environments using multiple animals.

Disclosures: **S. Ochi:** None. **H. Inada:** None. **N. Osumi:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.07/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIHR15HD099023
Charles Center, W&M

Title: Connecting mitochondrial dynamics to the fate of radial glial neural progenitor cells in the Xenopus laevis optic tectum

Authors: M. KETTELBERGER, *J. BESTMAN;
Col. of William and Mary, Williamsburg, VA

Abstract: Radial glial neural progenitor cells (NPCs) are the heterogeneous proliferating stem cell population that gives rise to all cells in the brain. These slender cells span the developing brain making contact with the ventricle and the outer pial surface. Early on, these highly

polarized cells divide symmetrically to expand this progenitor pool, but as development continues the NPCs begin to asymmetrically divide to produce neurons. Intrinsic and extrinsic cues guide this irreversible and critical fate switch. If regulated inappropriately, a premature shift to neurogenesis limits brain development and contributes to neurodevelopmental disorders. A feature of many stem cells is their reliance on non-mitochondrial ATP production. Yet, these cells contain dynamic and motile mitochondria. In some stem cells it has been shown that the metabolically mature older mitochondria are segregated during cell division so that they are preferentially inherited by the progeny that differentiate. It is not known whether NPCs also compartmentalize mitochondria leading up to division and how that distribution influences the fate of the progeny. To address these questions, we use in vivo time-lapse confocal microscopy to image fluorescent protein-labeled NPCs and their mitochondria in the optic tectum of albino Xenopus laevis tadpoles. This approach preserves the surrounding neural circuitry of the developing visual system and allows us to monitor and track the NPCs, their mitochondria, and their progeny over days in their natural environment. We find that mitochondria in the NPCs are motile and undergo fusion and fission. Our data suggest that mitochondria are not equally inherited when the NPCs divide. Using photo-activatable GFP to label subpopulations of mitochondria in NPCs within the 24 hours before cell division reveals high levels of mitochondria fusion and organelles that migrate >100 µms. Together our data show that mitochondria dynamics and distributions are biased as the NPCs prepare for cell division, suggesting that the position of the mitochondria may regulate the type of division.

Disclosures: M. Kettelberger: None. **J. Bestman:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.08/A18

Topic: A.08. Development of Neural Systems

Support: NIH Grant 1R15HD077624-01
NIH Grant 1R15HD096415-01
William and Mary Charles Center

Title: Molecular characterization of the tweety (ttyh) gene family

Authors: *A. WEST, M. ROYSTER, M. S. SAHA;
Col. of William and Mary, Williamsburg, VA

Abstract: This project explores the role of the tweety gene family member 1 (*ttyh1*), during development in the *Xenopus laevis* nervous system with potential future applications for biomedicine. *Ttyh1* is thought to encode for a Ca2+ -independent, volume-sensitive Cl- channel that is capable of binding Ca2+, however its Ca2+ independence is debated. *Ttyh1* has been linked to the Notch signaling pathway, which is highly conserved throughout vertebrate species

and crucial for regulation of cell fate, proliferation, neuroplasticity, and death during development. Previous work in the lab has shown that *ttyh1* is highly expressed in the adult and developing nervous system, an expression pattern that has implications for the maintenance of neural stem cells and numerous cellular functions, such as cell communication, adhesion, and migration. Differential expression of *ttyh1* has been implicated in various pathologies and cancers, in astrocytes following status epilepticus, as well as in acute nociception and pain sensitization.To elucidate the function of this gene, CRISPR-CAS9 was used to knock out *ttyh1*. We assessed the efficacy of the knockout using Tracking of Indels by DEcomposition Analysis (TIDE) and obtained 75% efficiencies and 85% survival (n=20). We analyzed the embryos via in situ hybridization at several different stages with *Sox2* (a marker for the proliferative neural stem cells) and NBT (*tubb2*) (neural beta tubulin, a marker for postmitotic neurons). Interestingly, while NBT is consistently downregulated, *Sox2* appears unchanged at earlier stages but downregulated at hatching stages (st. 30), suggesting a more complicated regulatory interaction between *ttyh1* and *Sox2*. These results suggest that *ttyh1* may be involved in neural stem cell development, but further investigation is needed to confirm its precise role. We also note that these results were confirmed using qRT-PCR. Additionally, we conducted qRT-PCR using *Notch1* and *ttyh3*, a gene family member of *ttyh1*. *Notch1* expression was not significantly affected in *ttyh1* CRISPR embryos, while *ttyh3* expression was upregulated at late neurula stages (st. 20) and downregulated by hatching stages (st. 30), suggesting that embryos may be mounting a compensatory response to the lack of *ttyh1* expression. Additionally, we have used bioinformatic analysis to analyze similarities in the upstream regions of *ttyh1* and *ttyh3* with the goal of identifying conserved regulatory elements. Intriguingly, the result of this indicates very little similarity between the upstream regions of these genes, suggesting complex modes of gene expression regulation.

Disclosures: A. West: None. **M. Royster:** None. **M.S. Saha:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.09/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: 5T32GM008056
F31NS120699
R01NS114510

Title: A Combinatorial Transcriptional Codes Drives the Specification of Phrenic Motor Neuron Identity

Authors: *R. KC[1], P. PHILIPPIDOU[2];
[2]Case Western Reserve Univ., [1]Case Western Reserve Univ., Cleveland, OH

Abstract: Breathing is essential for life. Phrenic motor column (PMC) neurons, which provide the final motor output of respiratory circuits, reside in the cervical (C2-C5) spinal cord and drive diaphragm activation necessary for breathing. We found that two *Hox5* genes, *Hoxa5* and *Hoxc5*, are specifically required for the establishment of PMC and control diverse aspects of PMC development including motor neuron (MN) clustering, intramuscular branching, and survival. However, the molecular mechanisms underlying Hox5-mediated transcription and target selectivity are not fully understood. Here, we find that Hoxa5 contributes to the accessibility of regulatory regions that are involved in developmental processes in cervical MNs. We further perform in vivo ChIP-seq analysis and show that a significant percentage of Hoxa5 ChIP-seq peaks are enriched around transcription start sites in cervical spinal tissue. Importantly, we find co-occupancy of these sites with the TALE protein cofactor Pbx1 in regions with a consensus Hox/Pbx composite motif (AT/ATTA/TC). Moreover, a database search using the Pbx1-Hoxa5 composite motif sequence returned a POU domain motif as our top hit. We further show that Hoxa5 physically interacts with Scip, a POU-domain transcription factor that is highly expressed in PMC neurons, and this interaction is independent of the YPWM domain of Hoxa5, which is used by Hox proteins to interact with TALE cofactors. Our results demonstrate that Hoxa5 alters chromatin accessibility and interacts with cofactors, such as Pbx1 and Scip, to regulate phrenic-specific transcriptional programs, and provide insights into how Hox5 proteins selectively induce phrenic MN identity.

Disclosures: R. Kc: None. **P. Philippidou:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.10/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: E0300101

Title: Inorganic arsenic induces motor neuron development via Sonic hedgehog pathway in zebrafish

Authors: *J. KANUNGO[1], B. ROBINSON[2], Q. GU[3], S. FITZPATRICK[4];
[1]Neurotoxicology, Natl. Ctr. For Toxicological Research/Food and Drug Admin., Jefferson, AR; [2]Natl. Ctr. For Toxicological Res., Natl. Ctr. For Toxicological Res., Jefferson, AR; [3]FDA Natl. Ctr. for Toxicological Res., FDA Natl. Ctr. for Toxicological Res., Jefferson, AR; [4]Ctr. for Food Safety and Applied Nutrition, U.S. Food and Drug Admin., College Park, MD

Abstract: Inorganic arsenic is a contaminant in foods and drinking water. Although inorganic arsenic is known to induce neurotoxicity, the mechanisms are not clear. Here, we investigated the effect of inorganic arsenic on early development of zebrafish including its effect on the motor neurons. Exposure of wild type zebrafish embryos at 5 hours post fertilization (hpf) to sodium

arsenite induced developmental toxicity as measured by body length in 72 hpf larvae, beginning at a concentration of 300 mg/L concentration. At 24 and 48 hpf, the embryo development appeared unperturbed. No mortality or overt morphological deformity was detected below 500 mg/L sodium arsenite. Excessive apoptosis throughout the body of the larvae was detected starting at 200 mg/L sodium arsenite. Heart rate remained unchanged at concentrations of 100 – 400 mg/L sodium arsenite. In vivo analyses of the *hb9-GFP* transgenic larvae, which express GFP in the motor neurons, demonstrated that both 200 and 400 mg/L sodium arsenite produced supernumerary motor neurons in the spinal cord. Inhibition of the Sonic hedgehog (Shh) pathway that is essential for motor neuron development, by Gant61, prevented sodium arsenite-induced supernumerary motor neuron development. The results show that inorganic arsenic can alter neurogenesis of motor neurons in a vertebrate animal model, which may have implications to human health.

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

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

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Topic: A.08. Development of Neural Systems

Support: Hampden-Sydney College Student/Faculty Summer Research Proposal
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Independent Technology Innovation Fund, Huazhong Agricultural University (Fundamental Research Funds for the Central Universities, Program No. 2662017QD032)
Zebrafish International Resource Center (ZIRC), for AB wild-type adult zebrafish

Title: Characterization of Rbfox1l and Rbfox2 RNA-binding protein expression in the larval zebrafish brain

Authors: *M. BERBEROGLU[1], M. MISCIKOWSKI[1], N. SINGH[2], F. MA[3];
[1]Hampden-Sydney Col., Hampden-Sydney, VA; [2]Valparaiso Univ., Valparaiso, IN; [3]Chinese Inst. for Brain Research, Beijing, Beijing, China

Abstract: RNA-binding proteins play an important role in alternative splicing events that impact the development and function of the nervous system. RBFOX1/Rbfox1 has been implicated in a

variety of neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorder (ASD), anxiety, epilepsy, schizophrenia, and attention deficit hyperactivity disorder (ADHD). RBFOX2/Rbfox2 is necessary for proper development of the cerebellum and in the organization of cerebellar Purkinje cells in mice. We have recently identified expression of RNA-binding protein Rbfox1l (Rbfox1-like) in the adult zebrafish brain, with expression in a restricted population of neurons within the central part of the dorsal telencephalon (Dc) region, and a smaller group of neurons within the medial part of the dorsal telencephalon (Dm) (Ma et al., 2019). We have also identified broad expression of Rbfox2 within neurons throughout the adult zebrafish brain, including expression of Rbfox1l and Rbfox2 within cerebellar Purkinje cells (Ma et al., 2019). Though the adult expression of Rbfox1l and Rbfox2 proteins has been characterized, expression of these RNA-binding proteins in the larval zebrafish brain is not well understood. In this study, we investigate the expression of Rbfox1l and Rbfox2 proteins in the larval zebrafish brain in conjunction with neuronal marker HuC/D. In contrast to Rbfox1l expression within the adult zebrafish telencephalon and cerebellum (Ma et al., 2019), Rbfox1l protein expression is not detected within the brain at the larval stage 7 days post-fertilization (dpf), n=3 brains. This finding parallels previous reports showing lack of brain expression observed by in situ hybridization for *rbfox1l* mRNA during larval stages up to 5 dpf in the literature, and further extends these findings to 7 dpf with an understanding of Rbfox1l protein expression. Additionally, our preliminary results suggest that Rbfox1l protein is not expressed in the brain at 3 dpf at the onset of larval development. Furthermore, we find that Rbfox2 protein is expressed broadly throughout the larval zebrafish brain at 7dpf, including expression within the cerebellum (n=3 brains), which is reminiscent of the broad expression observed within the adult zebrafish brain. Our preliminary results at 3 dpf also suggest broad expression of Rbfox2 protein throughout the brain. We will further confirm and characterize expression of Rbfox1l and Rbfox2 at stages 3 dpf and 7 dpf spanning early larval development. A better understanding of Rbfox1l and Rbfox2 protein expression during larval development may help us to interrogate *rbfox* gene function in brain development and in neurological disorders.

Disclosures: **M. Berberoglu:** None. **M. Miscikowski:** None. **N. Singh:** None. **F. Ma:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.12/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH EY015290
National Organization for Albinism and Hypopigmentation (NOAH)
António Champalimaud Vision Award
Simons Foundation Senior Fellow Award
Fight for Sight Postdoctoral Fellowship

Title: Does improper communication between the retinal pigment epithelium and retina affect neurogenesis in albinism?

Authors: M. DILLINGER, **M. LIAPIN**, N. SLAVI, *C. A. MASON;
Zuckerman Inst., Columbia Univ., New York, NY

Abstract: The binocular visual circuit is comprised of retinal ganglion cells (RGCs) projecting either ipsilaterally or contralaterally from the eye to the brain. Individuals affected by albinism display an abnormal distribution of ipsilateral and contralateral RGC axons, leading to poor stereopsis. The ciliary margin zone (CMZ), a neurogenic niche at the embryonic retinal periphery, is a source of ipsilateral RGCs that will express their signature transcription factor Zic2. The CMZ also expresses Cyclin D2, a key regulator of the neurogenic output of the CMZ (Slavi et al., 2023). The retinal pigment epithelium (RPE) is connected to the adjacent developing retina via gap junctions. However, the mechanism by which the RPE normally influences retinal precursor cells, and how this relationship changes in the absence of melanin in albinism is poorly understood.
To analyze how gap junctions influence retinal development, we blocked the communication between the RPE and the retina in pigmented and albino mice using a conditional mouse line that interfered with the gap junction protein Cx43 in the peripheral retina, through Pax6-alpha Cre (αCre;Cx43flox). We then determined the number of CyclinD2^{+} and CMZ-derived Zic2^{+} cells. We propose that the integrity of the RPE and communication channels is important for transmitting factors from the RPE to the neural retina to influence neurogenesis.
To begin to examine factors, both beneficial and deleterious, from the RPE that could influence neurogenesis in the neural retina, we performed proteomics on whole embryonic eyes. Initial GO analysis of albino and pigmented eyes revealed a significant change in expression of proteins that control cell proliferation, cell cycle transitions, and cell fate commitment. Strikingly, eight candidates upregulated in the albino eye respond to injury and inflammation, and specifically to IL-1b, IL-12, and NF-kB. Immunohistochemistry supports our observation of increased inflammation signals in the albino RPE.
From these analyses, we hypothesize that the albino retina may be in a state of inflammation and that the transmission of inflammatory signals from the RPE to the retina could influence the imbalance of ipsilateral and contralateral RGCs in the albino.

Disclosures: **M. Dillinger:** None. **M. Liapin:** None. **N. Slavi:** None. **C.A. Mason:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.13/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS 1T32NS115656-01A1
NIMH 1R21MH129995-01

Title: A developmental roadmap for the sexually dimorphic formation of the medial amygdala

Authors: *A. ABU IRQEBA[1], S. FELSEN[1], M. GOODRICH[2], Z. LI[1], T. HAYDAR[1], J. G. CORBIN[1];
[1]Ctr. for Neurosci. Res., [2]Children's Natl. Med. Ctr., Washington, DC

Abstract: Across vertebrate species, social behavior is controlled by an integrated brain system comprised of multiple cortical and subcortical structures. A central component of social circuitry is the amygdala. Dysfunction and misdevelopment of the amygdala is highly implicated a variety of human conditions characterized by deficits in social communication, such as autism spectrum disorder (ASD). A number of studies have implicated the medial subnucleus of the amygdala (MeA) as a critical brain region for processing social information. However, how the medial amygdala forms and how these developmental events unfold to guide circuit formation remain unknown. Here, we focus on the transcriptomic mechanisms that facilitate maturation of neurons destined for the MeA. To accomplish this, we carried out a large-scale temporal snRNA-seq experiment of the developing and adolescent MeA to follow neurons from cell genesis and during migration, sexual differentiation and circuit formation. Our dataset suggests a large-scale radiation event takes place at E16.5 with cells taking one of at least 6 distinct transcriptomic pathways; these pathways then collapse at P1 as neurons fine tune gene expression and make their way to their final identity. We detected 22 lineages known to contribute to the MeA at varying prevalence including those marked by Foxp2, Dbx1, Sim1, and Otp. Our analysis further uncovered novel sexually dimorphic neuronal populations. Future studies will be aimed at understanding the full repertoire of transcriptomic changes that underly MeA formation, dissecting the functional role of these genes in lineage progression and provide further insight into the timing of the emergence of sex differences.

Disclosures: A. Abu Irqeba: None. **S. Felsen:** None. **M. Goodrich:** None. **Z. Li:** None. **T. Haydar:** None. **J.G. Corbin:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

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Program #/Poster #: PSTR060.14/B1

Topic: A.01. Neurogenesis and Gliogenesis

Support: Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

Title: Supt4h, a transcription elongation factor, directs the development of rhythm generators in a lineage specific manner

Authors: *F.-Y. LIN[1,2], P.-N. LI[1], C.-K. SU[3], Y.-T. YAN[3], S.-J. CHOU[2,4], T.-H. CHENG[1,2,5];
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Univ. and Academia Sinica, Taipei, Taiwan; [3]Inst. of Biomed. Science, Academia Sinica, Taipei, Taiwan; [4]Inst. of Cell. and Organismic Biology, Academia Sinica, Taipei, Taiwan; [5]Brain Res. Center, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Differentiation of neural progenitor cells into a broad spectrum of cell types in the brain with diverse neural functions requires a precise spatial-temporal transcription of genes at the developmental stages. In our earlier studies, we demonstrated that Supt4h, a transcription elongation factor that facilitates the elongating RNA polymerase II stably across chromatin templates, is favorable for effective expression of genes in a DNA context dependent manner, yet its regulatory role in the neural development has so far remained elusive. Here, using multiple lines of *Supt4h* neural-specific conditional knockout (cKO) mice, we showed that Supt4h is specifically required for the genesis of pre-Bötzinger complex (preBötC), a nucleus located in the medulla that generates the inspiratory breathing rhythm. Genetic depletion of *Supt4h* in *Dbx1*- but not *Atoh1*-lineage cells results in a neonatal lethality caused by respiratory failure after birth. We observed that, under normal conditions, during the course of preBötC development, *Dbx1*-lineage cells migrate from the V0 ventricular zone to the L-V axis of the mantle zone in the medulla. However, such cell migration is greatly impaired in *Supt4h* cKO mice, which can be attributed in part by a decrease of *Dbx1*-lineage cells. Our findings suggest that Supt4h plays an important role in directing a subset of neural progenitor cells toward their terminal differentiation and Supt4h is essential for the development of preBötC by *Dbx1*-lineage cells.

Disclosures: F. Lin: None. **P. Li:** None. **C. Su:** None. **Y. Yan:** None. **S. Chou:** None. **T. Cheng:** None.

Poster

PSTR060. Mechanisms of Cell Fate

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.15/B2

Topic: A.01. Neurogenesis and Gliogenesis

Support: GAČR-20-06927S

Title: Transcriptional and epigenetic role of neurod1 in neuronal development in the inner ear

Authors: *L. LEBRÓN-MORA[1,2], M. TAVAKOLI[1,2], R. BOHUSLAVOVÁ[2], B. FRITZSCH[3], G. PAVLÍNKOVÁ[2];
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Abstract: The loss of auditory neurons leads to a permanent hearing impairment due to their little ability to regenerate. To prevent neuronal loss and achieve long-term maintenance of neurons, it is crucial to delve into the regulatory networks that control neuronal biological processes. NEUROD1, a bHLH pioneer transcription factor, plays a key role in cell fate specification, neurogenesis, and survival of auditory neurons. However, the molecular cues

underlying NEUROD1 function in the inner ear and its molecular regulation are at best incompletely understood. We generated a transgenic mouse model of conditional deletion of *Neurod1* and three mouse models of conditional overexpression of *Neurod1*. Using bulk RNA-seq, CUT&Tag-seq, immunohistochemical staining and 3D-light sheet microscopy we observed a dysregulated transcriptome and altered epigenetic landscape in mutant embryos, and we found that the ectopic expression of NEUROD1 induced neuronal fate in cells initially not committed to neurons. Taken together, these results indicate that NEUROD1 induces the expression of neuron-related genes in neuronal progenitors by modifying the epigenetic landscape, and that NEUROD1 expression and function is tightly temporally and spatially regulated. Further research on how NEUROD1 orchestrates auditory neuronal development will help clarify the path towards new and more efficient therapies for hearing impairment.

Disclosures: L. Lebrón-Mora: None. **M. Tavakoli:** None. **R. Bohuslavová:** None. **B. Fritzsch:** None. **G. Pavlínková:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.16/B3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant R35 GM131804
The Robert A. Welch Foundation grant BE-0017

Title: Phosphatidylinositol transfer proteins regulate neural stem cell self-renewal during neurogenesis

Authors: *J. ZHOU, S. HUR, V. BANKAITIS, Z. XIE;
Texas A&M Univ. Syst. Hlth. Sci. Ctr., COLLEGE STATION, TX

Abstract: Phosphoinositide signaling is a crucial regulatory mechanism for fundamental cellular processes in development and disease. In addition to enzymes involved in phosphoinositide biosynthesis and breakdown, phosphatidylinositol transfer proteins (PITPs) are the core components of this signaling pathway and are ubiquitously expressed in eukaryotes. PITPs are known for their ability to transport phosphatidylinositol (PtdIns) monomers between membrane bilayers in vitro, as well as their capacity to stimulate PtdIns-4-phosphate (PtdIns-4-P) biosynthesis in cells. PtdIns-4-P serves as a precursor for the biosynthesis of PtdIns-4,5-bisphosphate (PtdIns-4,5-P2) and PtdIns-3,4,5,-trisphosphate (PtdIns-3,4,5-P3), which directly mediate signaling at biological membranes. The biochemical activity of PtdIns-transfer is thought to be the mechanism by which PITPs function in cells, supporting phosphoinositide signaling by mediating the transport of PtdIns monomers between membrane bilayers. However, the validity of this model under physiological conditions in cells remains to be tested. To address this, we used the embryonic mouse neocortex as an experimental system to determine how

mammalian PITPs function in vivo. Our study demonstrated that class I StAR-related lipid transfer domain (START)-like PITPs, PITPNA and PITPNB, redundantly support the self-renewal of neural stem cells (NSCs) during mouse neocortical neurogenesis. Our functional rescue analyses showed that the PtdIns-binding/transfer activity of PITPNA/PITPNB is required but not sufficient for this function. Interestingly, replacing PITPNA/PITPNB with heterologous PITPs that are fully competent for PtdIns-transfer activity did not restore NSC self-renewal. Furthermore, we showed that GOLPH3, a PtdIns-4-P-binding oncoprotein at the trans-Golgi network, is a downstream effector regulating NSC self-renewal. Our findings suggest that PITPNA/PITPNB support NSC self-renewal by stimulating PtdIns-4-P signaling at Golgi membranes, rather than by transferring PtdIns-4-P monomers between membrane bilayers. These results shed new light on the in vivo function of mammalian PITPs and provide insight into the mechanisms by which phosphoinositide signaling regulates NSC self-renewal during neocortical neurogenesis.

Disclosures: **J. Zhou:** None. **S. Hur:** None. **V. Bankaitis:** None. **Z. Xie:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.17/Web Only

Topic: A.01. Neurogenesis and Gliogenesis

Support: UCOL-AFO-072/22

Title: Physical exercise restores neurogenesis affected by tactile deprivation

Authors: N. IBARRA-CASTANEDA[1,2], D. ZARATE-LOPEZ[1], V. LOPEZ-VIRGEN[1], J. GUZMAN-MUNIZ[1], N. MOY-LOPEZ[1], *O. GONZALEZ-PEREZ[3];
[2]PhD Med. Sci. Program, Sch. of Med., [1]Univ. de Colima, Colima, Mexico;
[3]Psicologia/University of Colima, Colima, Mexico

Abstract: Rodents have tactile sensory hairs, referred to as vibrissae, which allow them to explore the environment. Increasing evidence indicates that this vibrissal system modulates several aspects of hippocampal physiology. The privation of this sensory system produces a significant decrease in the neurogenesis of the dentate gyrus (DG) in the hippocampus. Physical exercise is an effective promoter of neurogenesis; therefore, it is possible that physical exercise helps recover the neurogenesis affected by sensory privation. This study aimed to determine whether Physical exercise increases neurogenesis in CD1 mice deprived of the vibrissal sensory system. Male and female CD1 mice were divided into four groups: sedentary control, exercised control, sedentary lesion, and exercised lesion. Infraorbital nerve surgery followed by a physical exercise protocol was done. Bromodeoxyuridine (BrdU) was injected to label proliferating cells in the dentate gyrus. A significant increase of BrdU+ cells was found in both exercised groups

compared to non-exercised controls. This data confirms that physical exercise can restore the proliferation of neurogenic cells affected by sensory deprivation.

Disclosures: **N. Ibarra-Castaneda:** None. **D. Zarate-Lopez:** None. **V. Lopez-Virgen:** None. **J. Guzman-Muniz:** None. **N. Moy-Lopez:** None. **O. Gonzalez-Perez:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.18/B4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH / NIA Grant R21 AG080248
NIH / NICHHD Grant R21 HD098498

Title: Long-lived chromatin-associated proteins in the developing postnatal mouse brain

Authors: *A. P. WILEN, E. K. BOMBA-WARCZAK, N. R. RAO, J. N. SAVAS;
Neurol., Northwestern Univ., Chicago, IL

Abstract: Most cellular protein lifetimes are measured in days or hours; however, long-lived proteins (LLPs) are exceptionally stable proteins that persist for months or more. We have previously identified LLPs in several tissues harboring long-lived cells including crystallin in eye lens cells, mitochondria cristae proteins in the heart, and proteins associated with the myelin sheath in the brain. We have also previously identified several nuclear LLPs including lamins, histones, and the core of the nuclear pore, but hypothesize that there is a larger, yet undiscovered pool of nuclear LLPs. Specifically, we hypothesize that during mouse development, there is an unexplored pool of LLPs that regulate gene transcriptional programs involved in development and persist for weeks to months. To investigate this possibility, we performed a two-generation in vivo pulse-chase experiment. Female mice were metabolically labeled for 10 weeks with chow highly enriched with ^{15}N amino acid precursors and were bred. Throughout breeding, gestation, and nursing their pups, the mice continued to eat the heavy chow. The second-generation pups were switched to normal chow at p21 and were sacrificed at t0, t7, t14, t21, t28, t60, and t120 days. Nuclei were isolated from the pups' brains using filtration and density gradient centrifugation, and the proteins were digested into peptides using trypsin. Through liquid chromatography with tandem mass spectrometry (LC-MS/MS), we identified and quantified both the fully ^{14}N and ^{15}N-labeled peptides and assessed protein turnover using fractional abundance. Interestingly we discovered a small panel of LLPs including important epigenetic modifiers, centromeric proteins, and proteins associated with the RNA polymerase II enzyme. Taken together, our results point to the basal transcription machinery and chromosomal proteins as members of a new, undiscovered subset of nuclear proteins that persist for weeks to months during development. Through their long-lived status, these proteins may be playing a key role in

the changes that take place during postnatal development by acting as scaffolds and recycled subcomplexes to speed up gene transcription.

Disclosures: A.P. Wilen: None. **E.K. Bomba-Warczak:** None. **N.R. Rao:** None. **J.N. Savas:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.19/B5

Topic: A.01. Neurogenesis and Gliogenesis

Support: DFG Grant 512746157

Title: Single cell transcriptomic analysis uncovers GABAergic identities in the brainstem

Authors: *Y. XIA[1], A. PATNAIK[2], K. CUI[3], E. ISIK[3], L. R. HERNANDEZ-MIRANDA[4]; [1]Inst. für Zell- und Neurobiologie Charite Universitätsmedizin Berlin, berlin, Germany; [2]Charite Universtätsmedizin Berlin, berlin, Germany; [3]Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Inst. für Zellbiologie und Neurobiologie, Charite Uviversitätsmedizin Berlin, Berlin, Germany

Abstract: GABAergic neurons play a crucial role in modulating neural networks in the nervous system, and their dysfunction is implicated in a wide range of neuropsychiatric disorders. Recent advances in single-cell transcriptomics have started to uncover multiple subtypes of neuronal classes for cells located mainly in the forebrain or the cerebellum. However, regions like the brainstem have received less attention. This is partially due to its intricate, although highly conserved, structural organization. Here, I have set out to define the neuronal diversity of brainstem GABAergic neurons using single-cell RNA sequencing. To this end, I used a fate-mapping approach to mark with the green fluorescent protein (GFP), all neurons with a history of *Lbx1* expression, a transcription factor that acts as a selector gene of GABAergic fates in the brainstem. Using 10X Genomics, I sequenced >20,000 GFP+ cells that differentially segregated into 9 distinct cell clusters according to gene expression patterns. Furthermore, I also investigated the function of *Lbx1* in specifying brainstem GABAergic neurons by analysis gene expression patterns of *Lbx1* mutant cells using also 10X Genomics. In summary, my study uncovers the neuronal diversity of brainstem GABAergic neurons.

Disclosures: Y. Xia: None. **A. patnaik:** None. **K. Cui:** None. **E. Isik:** None. **L.R. Hernandez-Miranda:** None.

Poster

PSTR060. Mechanisms of Cell Fate

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.20/B6

Topic: A.01. Neurogenesis and Gliogenesis

Support: P. Sloan Research Fellowship
Whitehall Foundation Research Award
NIH R01 Grant

Title: Cellular and molecular mechanism of mok-1 function in left-right neuronal asymmetry

Authors: *R. XIONG[1], X. WANG[2], C.-F. CHUANG[1];
[1]Dept. of Biol. Sci., Univ. of Illinois at Chicago, Chicago, IL; [2]Div. of Developmental Biol., Cincinnati Children's Hosp. Res. Fndn., Cincinnati, OH

Abstract: The developing nervous system generates a large diversity of cell types with distinct patterns of gene expression and functions. One way to establish neuronal diversity is to specify neuronal subtypes across the left-right axis. The *C. elegans* left and right AWC olfactory neurons communicate to specify asymmetric subtypes, AWC^{OFF} and AWC^{ON}. The default AWC^{OFF} is specified by a Ca^{2+}-regulated kinase cascade that is activated by influx of Ca^{2+} through the voltage-gated Ca^{2+} channel UNC-2/UNC-36. Intercellular communication between the two AWC neurons and other neurons through the NSY-5/innexin gap junction network antagonizes *unc-2/unc-36* Ca^{2+} signaling in the induced AWC^{ON} cell. Our recent data suggest that voltage- and calcium-activated SLO BK potassium channels *slo-1* and *slo-2* acts redundantly downstream of *nsy-5* to inhibit *unc-2/unc-36* Ca^{2+} signaling in the specification of AWC^{ON}. To identify the genes required for *slo-1* function in inhibiting *unc-2/unc-36* Ca^{2+} signaling for promoting AWC^{ON}, we performed a non-biased forward genetic screen to isolate *mok* (modifier of K^+ channel) mutants that suppress the *slo-1(gf)* $2AWC^{ON}$ phenotype (both AWC neurons become AWC^{ON}). *mok-1*(*vy11)*, one of the loss-of-function mutants identified from this screen, displays a $2AWC^{OFF}$ phenotype (both AWC neurons become AWC^{OFF}). We identified the mutation responsible for the *vy11* phenotype using whole genome sequencing. The analysis of our CRISPR/Cas9 knock-in of fluorescent markers in endogenous *mok-1* reveals that *mok-1* is expressed ubiquitously in many tissues including but not limited to neurons, glial cells, and hypodermal cells. Genetic mosaic analysis data suggest that *mok-1* functions non-cell autonomously in non-AWC cells to promote AWC^{ON}. Consistent with the data, our results from tissue-specific rescue of *mok-1(vy11)* mutants and tissue-specific degradation of MOK-1 protein in wild type support that *mok-1* function in hypodermal and/or glial cells is sufficient and required for the specification of the AWC^{ON} subtype. Taken together, our study identifies a novel non-cell autonomous mechanism by which signals from non-neuronal cells regulate neuronal differentiation.

Disclosures: R. Xiong: None. **X. Wang:** None. **C. Chuang:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.01/B7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF GRFP 1745302
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Yang Tan Collective at MIT
Hock E. Tan and K. Lisa Yang Center for Autism Research at MIT
K. Lisa Yang and Hock E. Tan Center for Molecular Therapeutics in Neuroscience at MIT
Stanley Center for Psychiatric Research at Broad Institute

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

Authors: *M. E. SCHROEDER[1], L. METZNER[2], D. MCCORMACK[3], K. LI[2], Q. ZHANG[2], H. ZANIEWSKI[2], K. LEVANDOWSKI[4], E. S. BOYDEN[2,5], F. M. KRIENEN[6], G. FENG[2]; [1]Brain and Cognitive Sci., [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]McGovern Inst. for Brain Res., McGovern Inst. for Brain Res. at MIT, Cambridge, MA; [4]Stanley Ctr. for Psychiatric Res., Broad Inst., Cambridge, MA; [5]Howard Hughes Med. Inst., Cambridge, MA; [6]Princeton Neurosci. Inst., Princeston Univ., Princeton, NJ

Abstract: Astrocytes are an abundant class of glial cells with critical roles in neural circuit assembly and function. Recent single-cell and earlier bulk RNA sequencing studies have demonstrated significant transcriptomic heterogeneity among astrocytes, particularly across brain regions (Morel et al., 2017; Zeisel et al., 2018, Batiuk et al., 2020, Lin et al., 2022; Siletti et al., 2022). However, the developmental trajectory of this heterogeneity and its conservation across species requires further systematic study. To this end, we used single-nucleus RNA sequencing to characterize the molecular diversity of brain cells across developmental stages (neonate, early adolescent, late adolescent, young adult, and late adult) and four brain regions (prefrontal cortex, motor cortex, thalamus, and striatum) in the mouse and marmoset brain (with at least 3 mice and 2 marmosets per region and developmental time point). We made an effort to employ consistent dissection strategies, sample preparation protocols, and sequencing technology across groups to enable clean comparison of biological differences with reduced technical artifacts, which are extremely difficult to remove *in silico* (Tran et al., 2020). Our analysis of over 100,000 single astrocyte nuclei revealed striking regional heterogeneity among astrocytes, particularly between telencephalic and diencephalic regions, at all developmental time points surveyed in both species. Top DEGs between telencephalic and diencephalic astrocytes, many of which were conserved across species, included genes functioning in calcium signaling and glutamatergic synaptic transmission, suggesting that regional astrocytes may be molecularly specialized to support their local neuronal circuits. Though astrocytes clustered separately by region already in neonates, portions of this region-specific astrocyte gene expression signature changed with age: we found several genes which were regionally differentially expressed in newborns but not

adolescents or adults, and vice-versa. More broadly, this cross-species, cross-development, cross-region molecular profile of brain cells using consistent experimental and computational methodology and represents a valuable resource for the field.

Disclosures: **M.E. Schroeder:** None. **L. Metzner:** None. **D. McCormack:** None. **K. Li:** None. **Q. Zhang:** None. **H. Zaniewski:** None. **K. Levandowski:** None. **E.S. Boyden:** None. **F.M. Krienen:** None. **G. Feng:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.02/B8

Topic: A.01. Neurogenesis and Gliogenesis

Support: STI2030-Major Projects 2021ZD0202300

Title: Prenatal Development of Astrocytes in the Human Cerebral Cortex

Authors: *M. YAN, C. ZHOU, T. LI, W. HUANG;
Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: The evolutionary expansion and complexity of the cerebral cortex shape the unique cognitive capabilities of humans. Despite advances in our understanding of neurogenesis during brain development, including prominent theories of the “inside-out” patterning and the “radial unit” lineage, the process of human astrogenesis remains shrouded in uncertainty. In order to study developmental trajectories of human astrocytes, we first consulted the published single-cell transcriptomic atlas of human developing cortex during mid-gestation (GW18-24). Using the Seurat software, we extracted distinct clusters of astrocytes and their progenitor types, which include early radial glia (early RG), outer radial glia (oRG), truncated radial glia (tRG), glial intermediate progenitor cells (G-IPCs), and astrocytes. We also reconstructed the developmental timeline and lineage relationships of astrocyte clusters and their progenitor types by Monocle analysis, and our revealed that early RG possess the capacity to differentiate into oRG and tRG. While the majority of tRGs give rise to astrocytes via G-IPCs, oRGs can differentiate into astrocytes either through G-IPCs or without an intermediate step. Subsequently, we conducted immunofluorescence staining in fixed human embryonic tissues ranging from GW16 to GW24. In GW16-17, we observed absence of astrocytes and G-IPCs, suggesting that the astrocyte differentiation has not occurred yet at this developmental stage. In GW18-20, we observed sparse astrocytes and G-IPCs in CP and SP, indicating the emergence of RG differentiation and the initiation of astrocyte maturation during this developmental period. Furthermore, in GW21-24, there was a rapid increase in the number of astrocytes and G-IPCs within the CP and SP, indicating a progressive maturation and amplification of astrocytes during this timeframe. Finally, we performed lineage tracing in cultured brain slices. Our preliminary results

demonstrated that oRGs in the OSVZ region have the ability to migrate upward into SP/CP, potentially participating in neurogenesis or astrogenesis. These findings provide valuable insights into the spatiotemporal dynamics of astrocyte development, highlighting the potential contribution of different progenitor types in shaping the astrocyte population within the developing human cortex.

Disclosures: **M. Yan:** None. **C. Zhou:** None. **T. Li:** None. **W. Huang:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.03/B9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01MH125956

Title: Identifying driver transcription factors of human astrocyte development

Authors: *S. N. LANJEWAR, C. SOJKA, A. SING, A. KING, S. SLOAN;
Human Genet., Emory Univ., Atlanta, GA

Abstract: Astrocytes play active roles as choreographers of synapse formation and neural circuit development. Neurons and astrocytes are derived from the same progenitor cells called radial glia, which sequentially produce neurons and then astrocytes. The timing of this transition, termed the “gliogenic switch”, is critical for proper brain development. Our goal is to uncover novel factors that control astrocyte development using human cortical organoids, which recapitulate the timing of the gliogenic switch observed in human fetal development. Transcription factors (TFs) are key modulators in cell fate determination. We utilized a Time Course Regulatory Analysis pipeline that pairs gene expression (RNA-sequencing) and chromatin accessibility (ATAC-sequencing) data at multiple timepoints surrounding the gliogenic switch to identify driver TFs that specifically regulate human astrocyte gene expression. Using this pipeline, we identified FOXG1 and LHX2 as candidate modulators of astrocyte development. Surprisingly, these TFs are well established regulators of neuronal development, indicating a potential repurposing of their function between neurogenesis and astrogenesis. To functionally test their roles, we overexpressed FOXG1 or LHX2 in radial glia isolated from primary human fetal tissue (GW18-21). Radial glia overexpressing FOXG1 or LHX2 both exhibit a significant upregulation of astrocytic genes and downregulation of neuronal genes, supporting an additional role for these TFs in shifting cell fate commitment towards astrogenesis. Ultimately, understanding the key drivers of the gliogenic switch will provide insight into how perturbations to the timing and production of astrocytes contribute to the pathogenesis of neurodevelopmental disorders.

Disclosures: **S.N. Lanjewar:** None. **C. Sojka:** None. **A. Sing:** None. **A. King:** None. **S. Sloan:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.04/B10

Topic: A.01. Neurogenesis and Gliogenesis

Title: The molecular identity and morphology of glia limitans superficialis astrocytes in mouse and human

Authors: *P. HASEL[1], M. L. COOPER[1], A. MARCHILDON[1], U. RUFEN-BLANCHETTE[1], R. D. KIM[1], T. C. MA[1,2,3,4], U. J. KANG[1,2,3,4], M. V. CHAO[1,4,5,6], S. A. LIDDELOW[1,3,4,7]; [1]NYU Grossman Sch. of Med., New York, NY; [2]Fresco Inst. for Parkinson's and Movement Disorders, New York, NY; [3]Parekh Ctr. for Interdisciplinary Neurol., New York, NY; [4]Dept. of Neurosci. and Physiol., New York, NY; [5]Dept. of Cell Biol., New York, NY; [6]Dept. of Psychiatry, New York, NY; [7]Dept. of Ophthalmology, New York, NY

Abstract: Astrocytes are a highly abundant cell type in the Central Nervous System (CNS). They perform critical homeostatic functions in health but undergo complex reactive transformations in disease. Astrocytes are now appreciated to fall into distinct subtypes, whose identity is at least in part driven by the brain area they occupy. Indeed, some astrocyte subtypes can occupy strategic anatomical domains such as periventricular, perivascular, and subpial spaces. Despite recent efforts in cataloguing CNS-wide astrocyte subtypes using large scale single cell or single nucleus RNA-sequencing (sc/snRNA-seq) and genome-wide spatial transcriptomics, the identities of previously anatomically- and histologically-defined astrocyte subtypes remain elusive. This is true for astrocytes that make up the *glia limitans*, a border tissue consisting of astrocytes that are predicted to provide protection to CNS cells from peripheral insults. The *glia limitans* can be further split into *glia limitans superficialis* and *glia limitans perivascularis*, indicating its association with either the brain surface or penetrating blood vessels, respectively, but whose molecular identities are unknown. Here, we integrate large scale scRNA-seq, spatial transcriptomics, light sheet microscopy and *in situ* hybridization to report the molecular identity of *glia limitans superficialis* (GLS) astrocytes in both mouse and human. We show that a transcriptionally continuous domain tracks the surface of the brain and spinal cord and delineates subcortical brain regions. We show that this domain is defined by highly specialized astrocytes that express a unique gene expression profile and selectively express the gene Myocilin (Myoc). Using light sheet microscopy, we show that *glia limitans superficialis* astrocytes possess an extraordinary morphology, with flat cell bodies tiling the cortical surface and branched processes protruding into the parenchyma. We show that the *glia limitans superficialis* is transcriptionally distinct from the *glia limitans perivascularis*, whose identity remains elusive. Interestingly, GLS astrocytes show a striking baseline reactivity indicative of interferon signaling, and GO term analysis indicates enrichment for genes involved in glial cell proliferation as well as lipid and sodium transport. Now that we have transcriptomic and ultimately genetic access to the *glia limitans superficialis*, we can profile their response to

diseases perturbing the brain and spinal cord surface, such as traumatic brain injury, stroke and spinal cord injury.

Disclosures: **P. Hasel:** None. **M.L. Cooper:** None. **A. Marchildon:** None. **U. Rufen-Blanchette:** None. **R.D. Kim:** None. **T.C. Ma:** None. **U.J. Kang:** None. **M.V. Chao:** None. **S.A. Liddelow:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.05/B11

Topic: A.01. Neurogenesis and Gliogenesis

Title: Determine the role of TDP-43 in postnatal brain development

Authors: *B. KUAH[1], A. I. CHEN[2], S.-C. LING[1];
[1]Natl. Univ. of Singapore, Singapore, Singapore; [2]Scintillon Inst., San Diego, CA

Abstract: TAR-DNA binding protein 43 (TDP-43) is a versatile DNA and RNA binding protein involved in a variety of biological processes including RNA metabolism, autophagy and organelle homeostasis. This multifunctional protein is implicated in neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), but the exact physiological role of TDP-43 in the central nervous system remains to be elucidated. We have previously reported that triglial dysfunctions in the spinal cords contributes to motor deficits in hGFAP-cre;TDP-43fl/fl (GFAP-cKO) mice, where TDP-43 deletion is restricted to the spinal cord astrocytes. In current study, we unexpectedly uncovered that TDP-43 is involved in the postnatal development of two brain regions, the dentate gyrus (DG) in the hippocampus and the cerebellum. Ex vivo whole brain structural magnetic resonance imaging (MRI) revealed a reduction in hippocampus and cerebellum volume, but not other brain regions. In both regions, we noticed a drastic change in the architecture - specifically a disruption in the DG radial glia and Bergmann glial. Within the dentate gyrus, there was a change in cellular proportions marked by a decrease in the radial glial cells and neuronal density as well as a concomitant increase in astrocytes. In the cerebellum, there was a reduction in Bergmann glial cells (BGCs) followed by an increased mislocalization within the molecular layer (ML). Furthermore, there was a reduction in stellate and basket cells density in the ML of the cerebellum. Cre-mediated deletion of TDP-43 appears to occur at DG radial glia and Bergmann glia based on a reporter line. Taken together, these results suggest that TDP-43 may be critical for development and maintenance of DG radial glia and Bergmann glia, which is essential for the proper formation of hippocampus and cerebellum.

Disclosures: **B. Kuah:** None. **A.I. Chen:** None. **S. Ling:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.06/B12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant R01NS104999

Title: The brafv600e mutation in postnatal radial glia alters glial development in cerebral cortex

Authors: V. SONI[1], *J. LO TURCO[2];
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Abstract: The MAPK/ERK signaling pathway regulates and mediates cell growth and is one of the most commonly altered pathways in human cancers. Multiple activating mutations have been discovered in the BRAF gene, with the most common oncogenic mutation found in low-grade glioma and ganglioglioma being BRAFV600E. In this study we investigated the effects of BRAFV600E in postnatal radial glial cells (RGCs) in the developing cerebral cortex in mice. To accomplish this we crossed the $BRAF^{CA}$ mice, B6.129P2(Cg)-*Braf*^{tm1Mmcm}/J, containing a conditional BRAFV600E alle, with the Ai9 mouse reporter line that conditionally expresses tdtomato after Cre expression. We electroporated Cre mRNA into RGCs of the dorsal lateral ventricles at P1-P2, and brains were analyzed at P9, P15, and P21. Our findings revealed that at P15 and P21 > 95% of tdtomato+ cells were glial cells, astrocytes, oligodendrocyte precursors, and oligodendrocytes in both $BRAF^{wt}$ and $BRAF^{CA}$ neocortex. Notably, by P21 we observed a large qualitative increase in the numbers of glial cells in $BRAF^{CA}$ compared to $BRAF^{wt}$ animals. The increase in glia in $BRAF^{CA}$ was particularly evident in the white matter where dense bands of tdtomato+ glia extended dense processes parallel to the ventricular surface. Additionally, at P21, in both mutant and wildtype animals, there were areas across cortical layers containing glial cells arranged in spatially distinct clusters. We quantified the number of cells in these clusters and found a significant increase in the number of glial cells/cluster in $BRAF^{CA}$ relative to $BRAF^{wt}$. Wildtype cluster sizes ranged from 2-7 glial cells with an average of 2.08 cells/cluster while in the $BRAF^{CA}$ mutant cluster sizes ranged from 3-23 cells with an average of 9.15 cells/cluster. This suggests BRAFV600E either initiates local clonal expansion in glial progenitors or that $BRAF^{CA}$ expressing cells preferentially cluster by migration. Collectively, these results indicate that expression of BRAFV600E in postnatal RGCs restricted to generating glial cells is sufficient to increase the numbers and change the spatial distribution of glial cells, potentially through clonal expansion. These alterations may represent a preneoplastic stage initiated by BRAFV600E in glial lineages within developing cerebral cortex.

Disclosures: V. Soni: None. **J. Lo Turco:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.07/B13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant-in-Aid for Early-Career Scientists, Japan Society for the Promotion of ScienceGrant-in-Aid for Early-Career Scientists, Japan Society for the Promotion of Science 23K14203
The 37th Research Exchange Grants, The Ichiro Kanahara Foundation for the Promotion of Medical Sciences and Medical Care

Title: Functional elucidation of the transcription factor MEIS1 during fate determination of cerebellar astroglial cells

Authors: *T. ADACHI[1], K. ICHIJO[1], T. OWA[2], J. KAIYUAN[1], M. MIZUNO[1,3], I. HASEGAWA[1], Y. U. INOUE[4], T. NAKAMURA[5], T. INOUE[4], M. HOSHINO[1];
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Abstract: Cerebellar astroglia can be divided into two subgroups: Bergmann glia (BG) localized in the Purkinje cell layer (PCL) and astrocytes localized in the inner granular cell layer (IGL) and white matter layer (WM). Recently, these two types of astroglia are known to be produced from a common progenitor cell, but it is not known what molecular mechanisms produce this difference in fate.Unlike normal astrocytes, BGs have two to three long unidirectional projections. In the mature cerebellum, BGs function as lining structures, and during development they serve as scaffolds for the migration of granule cells. Thus, BGs are astroglia with specialized morphology and function, but the detailed molecular mechanisms by which they acquire this specialization remain to be elucidated.The transcription factor Myeloid ectopic viral integration site 1 (*Meis1*) is a gene encoding a homeobox protein known to have various functions in nervous system development. However, the details of its function in astroglial cells are unknown. In this study, we specifically knocked out *Meis1* in the cerebellum and observed the phenomena of BG loss and the appearance of ectopically localized astrocyte-like cells. Further analysis by single-cell RNA-seq revealed that these astrocyte-like cells were most likely astrocytes, based on the characteristics of the expressed genes. Since there was no significant increase in cell death during development and no abnormalities in the number of astroglial progenitor cells during fetal life, it was thought that "cells that should have differentiated from astroglial progenitors into BG differentiated abnormally into astrocytes". A similar, but a bit mild phenotype was also observed when *Meis1* was knocked out specifically in astroglia of mice shortly after birth. Furthermore, we established a system in which only BG-like morphology progenitor cells localized in the PCL were labeled by electroporation. The results showed that BG-like progenitor cells give rise to both BGs and astrocytes, and that loss of *Meis1* biases their fate from BGs to astrocytes. We are now trying to elucidate how *Meis1* is involved in the

molecular mechanism of BG-like progenitor cell differentiation. We will also report some of the molecular mechanism we have already revealed.

Disclosures: **T. Adachi:** None. **K. Ichijo:** None. **T. Owa:** None. **J. Kaiyuan:** None. **M. Mizuno:** None. **I. Hasegawa:** None. **Y.U. Inoue:** None. **T. Nakamura:** None. **T. Inoue:** None. **M. Hoshino:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.08/B14

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 3RM1HG009491-03S2
NIH Grant R01EY033353
NIH Grant 1R21NS111186
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Title: Time series scRNAseq analysis in mouse and human informs optimization of rapid astrocyte differentiation protocol

Authors: *P. FRAZEL[1], D. LABIB[2], T. FISHER[1], R. BROSH[1], N. PIRJANIAN[2], A. MARCHILDON[1], S. LIDDELOW[1], J. BOEKE[1], V. FOSSATI[2];
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Abstract: Central nervous system macroglia (astrocytes and oligodendrocytes) are required for normal brain development and function, and are among the last cells to emerge during neurodevelopment. However, little is known about molecular mechanisms that underpin key decision points and dictate lineage commitment during gliogenesis. Here, we used single-cell RNA sequencing (scRNAseq) to analyze over 150,000 cells and nuclei across multiple timepoints during the differentiation of astrocytes and oligodendrocytes from human induced pluripotent stem cells (iPSCs) and mouse embryonic stem cells (mESCs). Using time series analysis of gene expression (Waddington optimal transport analysis), we identified genes involved in fate specification of glia in both species. We examined gene expression changes during intermediate states of glial specification and identified specific gene signatures of neuron and glia fates. Beyond gene expression, we used multiomic, dual snRNAseq/snATACseq analysis to uncover genomic regulatory sites mediating glial differentiation. These datasets will be useful for researchers interested in optimizing glial differentiation protocols in either species, and provide a window into human glial differentiation, difficult to study given its inaccessibility. To demonstrate the utility of this dataset, the time series scRNAseq analysis of mouse glial development was used optimize a rapid (<2 weeks) mouse astrocyte differentiation protocol that eliminates the embryoid body step. We tested the functional capacities of our rapidly-differentiated astrocytes across multiple physiological areas and show that the rapid-

differentiated cells respond like mature astrocytes. Particularly, differentiated cells displayed the ability to extend and develop morphological processes and change gene expression in response to both an inflammatory stimulus (TNF/IL-1a/C1q stimulation) and a wound assay (scratch test). Accordingly, these cells can be used to perform large-scale genetic screens for activators and inhibitors of the reactive astrocyte response to inflammatory or wound stimuli. To conclude, we also integrated our mouse scRNAseq dataset with a primary mouse brain atlas dataset and observed that differentiated cells share gene expression with early glia from primary mouse brain.

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Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.09/B15

Topic: B.09. Glial Mechanisms

Support: 5R25GM061151-21
R25NS080687

Title: Radial Glia-Like Cell Marker Expression in Echinoderm CNS Glia

Authors: *Y. MIRANDA-NEGRON, J. GARCIA-ARRARAS, G. RAMOS-LUGO;
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Abstract: Radial glia-like cells (RGLCs) are a key component of the central nervous system (CNS) regenerative response by providing a tissue with the capacity to generate new neurons and glial cells. In mammals, however, RGLC are mostly quiescent and are only found in specialized niches, making their study difficult. The cells are present in other animal groups, where they can mediate regenerative processes following injury. Our laboratory has used the sea cucumber *Holothuria glaberrima*, an echinoderm with amazing regeneration capacities, to study CNS regeneration. This organism has a population of RGLCs in its CNS that mediates the regeneration process. Although some studies have established a relationship between the echinoderm and vertebrate RGLCs, none has explored it at a molecular level. The present study aims to establish the relationship between these cells based on the presence of molecular markers. We first established a transcriptome database from *H. glaberrima* CNS, specifically from the radial nerve cords (RNC). We then used RGLCs sequences from rat, mouse, human, and sea urchin genomes that are used as markers of RGLCs and aligned them to our transcriptome database. Sequences obtained from these alignments were cross-validated using NCBI RefSeq, and a recently published H. glaberrima genome draft to determine if these were the holothurian homologues. Nine classical RGLC markers were found; all had E-values lower

than 1e-50, and half had 50% or higher identities. FISH-HCR was used to assess RGLC spatial marker expression. Thus, the combination of neuronal and RGLC markers allowed us to describe the cellular populations present in the holothurian CNS. Among our findings are (i) a neuron to glia ratio of 40% to 60% that correlates with what has been previously established. (ii) that 9.2% of our cells are exclusively STARD10^{+}(a neuronal marker), 33.2% exclusively immunoreactive to ERG1, and 29.7% with positive signals for STARD10 and ERG1 antibody. Most surprisingly, 27.8% cells do not belong to any ERG1 or STARD10 category. Additional subpopulation of cells are defined by other classical RGLC markers, including GLAST, PAX6, GS, and HES. Our results provide regional expression information and innovative insight regarding the potential heterogeneity of RGLC population in echinoderms CNS. Moreover, they clearly show the similarities at the molecular level between the RGLC cells of vertebrates and echinoderms.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Program #/Poster #: PSTR061.10/B16

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5K00ES033033-04
BWF Grant PDEP

Title: Environmental exposures shift radial glia cell fate away from gliogenesis

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[2]Cell Biol., [1]Emory Univ., Atlanta, GA

Abstract: Developmental toxicant exposures influence brain development by impacting cell fate, maturation and function. Using primary fetal brain and human induced pluripotent stem cell-derived 3D organoids, we demonstrate that prenatal exposure (2nd trimester) to the heavy metal lead (Pb) changes radial glia cell fate in the developing human brain. Chronic Pb exposure (3 weeks) increased the ratio of neurons to astrocytes in organoids. EdU labeling of newborn cells showed a decrease in astrogenesis and concomitant increase in neurogenesis in Pb-exposed organoids. Using single-cell RNA-seq and unbiased clustering a larger proportion of cells were assigned to the neuronal clusters and fewer to the glial clusters in Pb-exposed organoids. There was a strong transcriptional response to Pb in astrocytes and radial glia, but not neurons. In radial glia, there were changes in genes associated with metabolism, cell fate, cell commitment, BMPs and WNT signaling. To test whether Pb alters radial glia differentiation, we isolated radial glia from primary human fetal tissue (GW16-21, 2nd trimester) and quantified cell fate following exposure to Pb. We found no change in neurogenic cell divisions, but a ~50% decrease in astrogenic divisions. Additionally, cell tag lineage tracing barcodes and single cell sequencing

allowed us to isolate newborn cells clones derived from fetal radial glia. Ongoing experiments are focused on the mechanism by which Pb-induced transcriptomic and metabolic changes drive radial glia cell fate. Overall, these data suggest that prenatal Pb exposure may influence the cellular balance of neurons and astrocytes in the developing brain, which could contribute to Pb-associated cognitive, affective, and behavioral deficits later in life.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Topic: A.01. Neurogenesis and Gliogenesis

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Sontag Foundation Distinguished Scholars Award
NARSAD Young Investigator Grant
R01 ES027859
P30ES019776
NIH F32 ES031827

Title: Divergence from the human astrocyte developmental trajectory in glioblastoma

Authors: *C. SOJKA[1], H.-L. V. WANG[1], Y. LI[1], P. CHOPRA[1], T. N. BHATIA[1], A. SING[1], A. VOSS[1], A. KING[1], F. WANG[1], K. JOSEPH[3], V. RAVI[3], J. OLSON[2], K. HOANG[2], E. NDUOM[2], V. CORCES[1], B. YAO[1], S. A. SLOAN[1];
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Abstract: Glioblastoma (GBM) is defined by heterogeneous and resilient cell populations that closely reflect neurodevelopmental cell types. While it is clear that GBM echoes early and immature cell states, identifying the specific developmental programs disrupted in these tumors has been hindered by a lack of high-resolution trajectories of CNS developmental lineages. Here, we delineate the course of human astrocyte maturation to find where GBM astrocyte populations diverge. We generated a transcriptomic and chromatin accessibility map of human astrocyte maturation using cortical organoids maintained in culture for nearly two years. We chronicled a multi-phase developmental process orchestrated by a series of transcription factor and gene regulatory networks including a novel and molecularly distinct intermediate stage of human astrocyte maturation that separates proliferating progenitor from quiescent mature states. This intermediate stage serves as the site of developmental deviation in IDH-wildtype neoplastic

astrocyte lineage cells. Interestingly, IDH1-mutant tumor astrocytes are the exception to this developmental perturbation, as they reflect a substantially more mature signature than IDH-wildtype astrocytes. We propose that this maturation preservation is likely a consequence of IDH1mt-associated epigenetic dysregulation and identified biased DNA hydroxymethylation (5hmC) in maturation genes as a possible protective mechanism. Together, this study illustrates a novel cellular state aberration in GBM astrocyte lineage cells and presents new developmental targets for experimental and therapeutic exploration.

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Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NEI 5R01EY031445
NIH NEI 2R01EY030611
Hartwell Biomedical Fellowship

Title: An explant assay to investigate astrocyte-guided retinal angiogenesis

Authors: *J. VALDEZ-LOPEZ, S. ZARNICK, A. MILTNER, J. KAY;
Duke Univ., Durham, NC

Abstract: Angiogenesis is a central event in nervous system development that is essential for neural function. In retinal development, angiogenesis initiates from the optic nerve in the central retina and proceeds radially outward through the nerve fiber layer—the innermost retinal layer consisting of retinal ganglion cell axons and a network of developing astrocytes. Astrocyte development occurs prior to angiogenesis and is critical for guiding the growing vasculature, as astrocytes form a physical template that guides endothelial tip cells. Astrocytes are also the essential source of VEGF-A, a key molecule required to initiate angiogenesis. However, the signals that advance the wavefront, and guide endothelial tip cells along the astrocyte template, are unknown. Thus, identifying novel astrocyte-derived angiogenic cues can reveal basic mechanisms that apply throughout the nervous system while also yielding new molecular targets that could be exploited to treat vascular diseases in the retina. Our strategy to identify these cues is the following. First, we performed single-cell RNA-sequencing on purified retinal astrocytes, thereby identifying candidate genes selectively expressed in pro-angiogenic immature astrocytes localized ahead of the vascular wavefront. Second, to test the function of these genes, we are developing an explant overlay assay. Candidate genes are expressed in HEK293 cells, which are

then plated on top of acute retinal explants from P4/5 mice. Explants are then cultured overnight or for 8 hrs. In these co-cultures, retinal explants display healthy astrocytic networks and robust endothelial tip cells at the vascular wavefronts. Using HEK cells expressing VEGF-A as a positive control, we found evidence that molecules secreted from HEK cells can affect filopodial growth patterns in this assay. Therefore, this assay shows promise for screening candidate angiogenic genes. Identification of new molecules using this assay holds promise for illuminating new mechanisms of glial-vascular interactions during development, providing new targets for further study or therapy.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Program #/Poster #: PSTR061.13/B19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY030611-04

Title: How do blood vessels trigger retinal astrocyte differentiation?

Authors: *A. MILTNER[1], C. PAISLEY[3], S. MARTINEAU[1], J. KAY[2];
[1]Neurobio., [2]Duke Univ., Durham, NC; [3]Neurobio., Duke Univ. Neurobio. Grad. Program, Durham, NC

Abstract: During retinal angiogenesis, astrocytes are born at the optic nerve head; migrate peripherally; and establish a physical template and produce growth factors necessary to guide vascular development. As endothelial cells grow over the astrocyte template, astrocytes are exposed to vessels and oxygen. This triggers a major phenotypic switch, downregulating pro-angiogenic precursor genes and triggering astrocyte differentiation. The precise nature of these phenotypic changes, as well as the mechanisms controlling them are unknown. One reason these changes are so poorly characterized is that, at any given developmental time, both precursor and mature astrocytes are present in the retina, precluding bulk transcriptomic analysis. Canonical precursor and mature astrocyte gene expression coincides with vessel arrival, and some genes are known to be directly regulated by oxygen. However, many astrocyte behaviors, and the transcriptional networks behind them, remain poorly understood. To overcome this challenge, we performed single-cell RNA-sequencing and identified cell states corresponding to both precursor and mature astrocytes. Astrocytes were FACS-purified (Fluorescence Activated Cell Sorting) from early (postnatal day 2 (P2)), middle (P5), and late (P8) stages in mouse retinal angiogenesis and sequenced on the 10x platform. We identified numerous new markers of the precursor and mature astrocyte states and validated their selective expression in astrocytes ahead or behind the vascular wavefront using *in situ* hybridization on whole mount neonate mouse retinas. Surprisingly, we also identified the pro-neural transcription factor Achaete-scute homolog 1

(Ascl1) as being transiently expressed in a subset of astrocytes. Antibody staining for Ascl1 revealed that it is expressed in a subset of both mature and precursor astrocyte populations, making its expression pattern unique compared to the other markers identified in our study. Lineage tracing using an Ascl1CreER mouse crossed with a nuclear GFP reporter suggests Ascl1 is expressed transiently in retinal astrocytes. Ascl1 is known to be expressed in the final cell division in progenitors in other parts of the central nervous system, therefore it may be involved in specifying the timing of terminal astrocyte precursor divisions. The transcriptional networks identified in this study may reveal genetic pathways used elsewhere in the central nervous system to control astrocyte number, and present opportunities for new therapeutic research to directly target developmental astrocyte and vascular biology in the retina.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.14/B20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY030611
Holland-Trice Graduate Student Fellowship

Title: Cell-surface signals on developing retinal astrocytes promote their elimination by microglia

Authors: *C. E. PAISLEY[1], J. N. KAY[2];
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Abstract: Developmental cell death is essential for nervous system development. While developmental neuron death has been studied extensively, astrocyte death has often been overlooked. Our lab recently showed that astrocytes in the developing retina undergo an unusual non-apoptotic form of death that eliminates a vast proportion of the original population: We found that microglia are the major effectors of astrocyte death. However, the mechanisms that induce microglia to kill astrocytes remain mysterious. It is important to understand these astrocyte death mechanisms because astrocytes play a crucial role in patterning the retinal blood vessel network. Developmental perturbations to astrocyte number have large effects on their patterning, and in turn cause severe vascular patterning defects - some of which resemble human blinding disorders. We therefore sought to identify the non-apoptotic mechanisms that drive astrocyte death. Previous data suggested that astrocytes themselves are the source of cues that drive their own death via recruitment of phagocytic microglia. Here we identify the membrane lipid phosphatidylserine (PtdSer) as one such astrocyte-derived "eat-me" cue. PtdSer is best known as an "eat-me" signal expressed on the surface of apoptotic cells. We show that PtdSer is also externalized on the cell surface of apparently normal astrocytes during development.

Moreover, using a genetic approach to increase cell-surface PtdSer, we show that it is sufficient to drive astrocyte death. For these studies, we used an astrocyte-specific mouse knockout of Tmem30a, an obligate subunit of the flippase enzymes that remove PtdSer from the cell surface. In these knockout animals, microglia are recruited to Tmem30a mutant astrocytes, engulf them, and cause a significant acceleration of cell number decline. This excess astrocyte loss has functional consequences for the development of the vasculature: The astrocytic template for angiogenesis is overly sparse, leading to vascular patterning defects and delayed angiogenesis. These defects can be rescued by blocking the function of MFGE8, an opsonin that binds PtdSer and serves as a ligand for microglial phagocytic receptors. These findings implicate PtdSer exposure, and consequent microglial engulfment activity, as mechanisms underlying astrocyte death. Altogether our findings highlight the importance of astrocyte death for spatial patterning of the vasculature. Understanding how astrocyte population size is controlled will provide new insights into death mechanisms that are crucial for development not only in the retina, but may also sculpt glial populations elsewhere in the central nervous system.

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Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

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Program #/Poster #: PSTR061.15/B21

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI JP21K07309

Title: Erratic and blood vessel-guided migration of astrocyte progenitors in the cerebral cortex

Authors: *H. TABATA[1,2], M. SASAKI[2], M. AGETSUMA[3], H. SANO[2], H. YUKI[2], M. MIYAJIMA[2], K. HAYASHI[2], T. HONDA[2], M. NISHIKAWA[1], Y. INAGUMA[1], H. ITO[1], H. TAKEBAYASHI[4], M. EMA[5], K. IKENAKA[6], J. NABEKURA[2], K.-I. NAGATA[1], K. NAKAJIMA[2];
[1]Inst. For Dev. Res., Aichi Dev Disability Ctr., Aichi, Japan; [2]Keio Univ. Sch. Med., Tokyo, Japan; [3]Div. of Homeostatic Develop., Natl. Inst. For Physiological Sci., Okazaki, Japan; [4]Div. of Neurobiol. and Anatomy, Grad. Sch. of Med. and Dent. Sciences, Niigata Univ., Niigata, Japan; [5]Res. Ctr. for Animal Life Science, Shiga Univ. of Med. Sci., Shiga, Japan; [6]Natl. Inst. Physiological Sci., Okazaki, Japan

Abstract: Astrocytes are one of the most abundant cell types in the mammalian brain. They play essential roles in synapse formation, maturation, and elimination. However, how astrocytes migrate into the gray matter to accomplish these processes is poorly understood. Here, we show that, by combinational analyses of *in vitro* and *in vivo* time-lapse observations and lineage traces, astrocyte progenitors move rapidly and irregularly within the developing cortex, which we call erratic migration. Astrocyte progenitors also adopt

blood vessel-guided migration. These highly motile progenitors are generated in the restricted prenatal stages and differentiate into protoplasmic astrocytes in the gray matter, whereas postnatally generated progenitors do not move extensively and differentiate into fibrous astrocytes in the white matter. We found Cxcr4/7, and integrin β1 regulate the blood vessel-guided migration, and their functional blocking disrupts their positioning. This study provides insight into astrocyte development and may contribute to understanding the pathogenesis caused by their defects.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Topic: A.01. Neurogenesis and Gliogenesis

Support: National Natural Science Foundation of China Grant 82203429
China postdoctoral science foundation Grant 2021M690693
China postdoctoral science foundation Grant 2022T150136

Title: Rack7-mediated epigenetic regulation in brain tumor and development

Authors: *F. JIAO;
Fudan Univ., Shanghai, China

Abstract: High-grade brain tumors, including glioblastoma (GBM), have become the leading cause of cancer related death in children and adolescents. The 5-year survival of GBM is less than 5% due to limited diagnoses and treatments. Therefore, it is important to discover and research new tumor molecular biomarkers and therapeutic targets. We focused on the “driver mutations” in histone H3.3, which composed of H3K27M mutations in DIPGs and H3.3G34R/V mutations in GBM. In our previous project, we discovered and proved the chromatin recognition protein RACK7 specifically reads the histone H3.3G34R mutation. We also provide the structure data of RACK7-H3.3G34R complex. Based on these, we established a mouse neural stem cell model expressing H3.3G34R mutation to further research the potential role of RACK7 on tumorigenesis drove by histone H3.3G34R mutation. We carried out RACK7 ChIP-seq in wildtype (WT) or H3.3G34R-mutated(G34R) cell, and found that RACK7 preferred G34R-mutated chromatin. Also,we identified higher RACK7 ChIP signals at active enhancers marked by H3K4me1 and H3K27ac in G34R cells than in WT cells. Interestingly, we noticed the increased binding of RACK7 on *Fbxw7* enhancers, which always work as tumor-suppressor in cancers and have been detected loss-of-function mutations in pediatric GBM patients with

histone H3.3G34R mutation. To further investigate the function of *Rack7*, we next knock-out *Rack7* in WT and G34R cells. The transcriptome analysis show that RACK7 recognizes H3.3G34R mutation to suppress genes associated with neural differentiation program. We also found the protein levels of N-MYC and C-MYC are elevated in the H3.3G34R cells. These data shows *Rack7* work with H3.3G34R might drive the cells to tumorigenesis. Based on this, we performed *in vivo* tumorigenesis assays in mice brain. Our MRI results demonstrate that H3.3G34R expressing cells form larger tumors than cells expressing wildtype H3.3. Importantly, this tumor-promoting activity is compromised when RACK7 is knocked out or replaced by the H3.3G34R binding-defective mutant. Besides, considering *Rack7* may have function on neuronal or glial cell differentiation, we knocked out *Rack7* in mice brain through insert loxp sequences in *Rack7* genomic locus and recombination with multiple Cre-mice targeting different central nervous cell type. The knockout mice exhibited smaller body size and shorter lifetime. The slides staining of mice brain and transcriptome analysis of different cell type shows *Rack7* regulates genes associated with brain development. In summary, our results help to know the potential role of RACK7 in tumorigenesis and brain development from molecular to mice.

Disclosures: F. Jiao: None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.17/B23

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS K22NS09267
NINDS R01NS121660
UNM SOM RAC Grant
NCI P30CA118100

Title: Ascl1 regulates astrocyte and oligodendrocyte cell fate, proliferation, and migration in the dorsal cortex

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Abstract: Astrocytes and oligodendrocytes, key glial cell types in the mammalian CNS, play crucial roles in supporting neuronal function, modulating synaptic activity, and maintaining cerebral homeostasis. Despite this, the mechanisms underlying their specification, migration, and proliferation are complex and not fully understood. The basic-helix-loop-helix (bHLH) transcription factor ASCL1 is crucial for neurogenesis and gliogenesis in the ventral telencephalon, yet its specific role during glial development in the dorsal cortex remains less

explored. Here, we characterized the pattern of ASCL1 expression from the ventricular zone (VZ) to the cortical plate in E17.5, P0, and P2 stages, which are the onset of gliogenesis in the dorsal cortex of mice. Our findings revealed that across the three stages, ASCL1 expression begins in glial progenitor cells (GPCs) in the VZ and increases in migrating glial precursor cells within the corpus callosum and intermediate zone (CC/IZ). As these cells continue migrating towards the cortical plate, ASCL1 expression diminishes, exhibiting a transient expression pattern. Crucially, we observed that only a subset of ASCL1+ cells co-express OLIG2 in the CC/IZ and cortical plate. This suggests that ASCL1 plays a major role in the early and intermediate stages of GPC migration and differentiation before the cells commit to specific lineages and reach the upper cortical plate. We took advantage of the transient expression of ASCL1 to subsequently trace and "birthdate" the lineage of ASCL1+ GPCs at E17.5, P0, and P2 using the CreER-loxP system (*Ascl1CreERT2* knock-in x *Ai14-tdTomato* reporter mice), then examine the fate and distribution of the progenies at P30 in the dorsal cortex. *In vivo* fate mapping revealed that ASCL1+ GPCs give rise to both astrocytes and oligodendrocytes that populate the cortex and corpus callosum in all stages. Interestingly, the progenies of GPCs from E17.5 to P2 exhibited an 'outside-in' pattern of gliogenesis in the dorsal cortex, which is a stark contrast to the 'inside-out' pattern of neurogenesis. Furthermore, the majority of astrocytes and oligodendrocytes populating the corpus callosum were derived predominantly from P0 and P2 GPCs, not from E17.5. Finally, using conditional knock-out and overexpression strategies for *Ascl1*, we found that the loss of ASCL1 reduced the number and migration of both astrocytes and oligodendrocytes, whereas a sustained high level of ASCL1 is essential to activate OLIG2, thereby committing GPCs towards an oligodendroglia lineage. In conclusion, our study demonstrates that ASCL1 is the direct orchestrator of glial cell fate, migration, and proliferation in the dorsal cortex.

Disclosures: **L.E. Paez-Beltran:** None. **B.L. Myers:** None. **M. Liyanapathirana:** None. **E. Villicana:** None. **H. Chen:** None. **T.Y. Vue:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.18/B24

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSERC
CIHR
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Brain Canada
SickKids

Title: The effects of disrupting oligodendrogenesis during development

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Abstract: Introduction: Myelination of the brain begins shortly after birth, rapidly increases in early life, and then continues at a slower rate into adulthood, but the specific timing varies among brain structures. Myelin is an extension of the plasma membrane of oligodendrocytes (OLs), which arise from oligodendrocyte precursor cells (OPCs). Here, we explore the effects of halting OPC differentiation during development on white matter microstructure in mice. **Hypothesis:** We hypothesized that mice with halted OPC differentiation, particularly at a younger age, would have decreased white matter volume and increased diffusivity, compared to controls. **Methods:** This study used Myrf$^{fl/fl}$:NG2-creER^{TM} mice, in which the *Myrf* gene can be deleted from OPCs in Cre+ mice through the administration of tamoxifen, thereby halting the generation of new OLs in a time-controlled manner. Mice were administered tamoxifen at 3 or 5 weeks of age and were prepared for ex vivo MRI or electron microscopy (EM) 2 weeks later. MRI was performed on a 7T scanner with a multi-shell diffusion-weighted protocol to obtain metrics related to white matter microstructure and brain structure volumes. Analyses were restricted to the anterior commissure, corpus callosum, and optic tracts, based on these structures varying in their degree of myelination over the age range in the study. Group comparisons were made using linear mixed effects models with main effects for age, sex, and Cre status, interactions where significant, and random intercepts for cage. **Results:** The volumes of the anterior commissure and corpus callosum followed the expected trend, with younger Cre+ mice having smaller volumes than Cre- mice. No difference was observed in the volume of the optic tract, consistent with it having completed myelination earlier. Unexpectedly, no significant effect of Cre was observed in any of the diffusion MRI metrics, although a significant decrease in diffusivity with age was observed. Preliminary analysis of EM images from the anterior commissure suggests that male Cre+ mice have greater axonal density, primarily due to more unmyelinated axons, and that the myelinated axons are larger in diameter with thinner myelin. These trends are not apparent in the female mice. **Conclusions:** Changes in axon caliber, density, and myelination occur simultaneously during development, which may complicate the interpretation of diffusion MRI metrics. This data suggests that disrupting oligodendrogenesis during development affects axonal properties, possibly in a compensatory manner or perhaps due to disruption in the communication between myelin and axons that is involved in normal white matter development.

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PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.19/B25

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST 109-2314-B-006-015-MY3
MOST 111-2811-B-006-020

Title: Increasing interleukin-33 expression rescues oligodendrocytes from maturation impairment caused by exposure to cuprizone.

Authors: *H.-T. HUANG, S.-F. TZENG;
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Abstract: Our previous studies have demonstrated the crucial role of IL-33 in promoting the maturation of oligodendrocytes (OLs), and we aimed to investigate its potential therapeutic effects. In this study, we focused on the functions of interleukin-33 (IL-33) in cuprizone (CPZ)-induced demyelinating mouse models, which are associated with the progression of neuroinflammatory or neurodegenerative diseases. We examined the downregulation of corpus callosal adenomatous polyposis coli (APC)-positive cells in mice fed with CPZ for 6 and 8 weeks. Notably, the decrease in IL-33-positive cells was observed specifically in the corpus callosum, while no such decline was observed in the internal capsule. Furthermore, we conducted experiments using primary oligodendrocyte precursor cells (OPCs) and mature OLs treated with CPZ. After CPZ treatment, we observed a decrease in the expression of myelin basic protein (MBP) in the cultures of mature OLs. Similarly, both IL-33 mRNA and protein levels were downregulated. We also employed a lentiviral vector to overexpress IL-33 in OLs, aiming to counteract the lower levels of IL-33 induced by CPZ. Remarkably, when compared to that observed in OL mock culture, the overexpression of IL-33 in OLs resulted in a more pronounced membranous shape following CPZ treatment. Additionally, we observed an improvement in MBP protein levels. These findings suggest that IL-33 has the ability to defend against CPZ-triggered damage and promote OL homeostasis. Overall, our study highlights the significance of IL-33 in the context of demyelinating diseases and provides insights into its potential therapeutic implications for promoting remyelination and maintaining oligodendrocyte function.

Disclosures: H. Huang: None. **S. Tzeng:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.20/B26

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH K22NS104234
Robert J. and Nancy D. Carney Endowment

Title: A Potential Role for Extracellular Matrix in the Initiation of Optic Nerve Oligodendrocyte Differentiation

Authors: *G. MOLICA, J. AGUILERA, S. FREGOSO, S. MAYORAL;
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Abstract: Myelin is an insulating sheath that wraps axons allowing for quick, efficient neuronal communication. Oligodendrocytes (OLs) are the myelinating cells in the central nervous system. The capacity to myelinate depends on the differentiation of oligodendrocyte precursor cells (OPCs) into mature OLs. During development, OPCs migrate into the optic nerve (ON) soon after birth and proliferate. A few days later (~postnatal day 5), differentiation of OPCs into mature OLs begins. This timely switch in cellular programs suggests that there is some dynamically changing signal that initiates this onset of OL differentiation. Furthermore, this timeline of oligodendroglia (OLG) development is preserved even in the absence of neuronal signaling suggesting a major contribution from non-neuronal signals. To investigate these signals and their source, we sequenced mRNA transcripts from the nuclei of postnatal day 2 (P2) – prior to OL differentiation – mouse ONs and P7 – following OL differentiation – ONs. Single nuclei sequencing revealed the major cell type composition of the optic nerve with the most populous cell type being astrocytes. Differential expression (DE) analysis of the whole data set between P2 and P7 showed upregulation of transcripts encoding for extracellular matrix (ECM) proteins. Meanwhile, DE analysis of the astrocyte cluster revealed the ECM protein *Sned1* (sushi, nidogen, EGF-like domains 1) as the top differentially expressed gene. We hypothesize that a developmental change in ECM composition influences OL differentiation and that astrocyte-secreted Sned1 plays an important role in altering ECM structure or interacting directly with OPCs to influence differentiation. Additionally, other differentially expressed ECM transcripts are OLG-derived, suggesting a complex relationship for OLG in their own developmental trajectory. Through RNAscope *in situ* labeling of mRNA transcripts, we confirm the expression of *Sned1* in astrocytes. Furthermore, through qPCR analysis we confirm the differential expression of other ECM mRNA transcripts in ON tissues. Altogether, this makes a case for continuing to study changing ECM proteins in the ON and their potential impact on OL differentiation. Future studies will examine the combinatorial effect of these ECM proteins on primary OPCs *in vitro*. Overall, this work will uncover the roles that ECM plays on OLG during development with hopes for broader application to contexts such as injury and disease.

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PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.21/B27

Topic: A.01. Neurogenesis and Gliogenesis

Title: Human Induced Pluripotent Stem Cell-Derived Schwann Cell Precursors for Modeling Peripheral Neurobiology

Authors: *G. MCCABE, V. TRUONG, P. WALSH;
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Abstract: Schwann cells are the primary glia within the peripheral nervous system where they associate with and myelinate both sensory neurons and motor neurons. These three cell types are implicated in various human diseases - including diabetic peripheral neuropathy, Charcot-Marie-Tooth syndrome, and pain - yet these diseases have been difficult to study in a human-relevant context due to lack of well characterized translational in-vitro models. Here we demonstrate the rapid and efficient production of Schwann cell precursors (SCPs) from human induced pluripotent stem cells using directed differentiation under defined media conditions in 10 days. These SCPs were characterized via immunocytochemistry and qPCR for the markers OCT6, SOX10, S100B, and KROX20. To develop complex models of peripheral neurobiology, SCPs were co-cultured with sensory neurons and motor neurons derived from the same human induced pluripotent stem cell line using 7 day directed differentiation protocols. SCP-axon alignment was showcased after only one week in vitro, and myelination markers myelin basic protein and myelin protein zero were analyzed at multiple timepoints. Functional characterization of the co-cultures using multi-electrode arrays and calcium imaging were explored. In summary, the ready availability of these hPSC-derived SCPs and sensory/motor neurons will rapidly advance the development of more physiological models for human peripheral nervous system diseases.

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

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PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.22/B28

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS104994

Title: Characterizing the postnatal development and maturation of mouse cerebellar microglia

Authors: M. MARTINEZ[1], W. REMILLARD[2], L. WALSH[1], *I. SOTO REYES[3];
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Abstract: Previous studies in our laboratory found that changes in microglia morphology, phagocytic activity, and expression of developmental proteins linked to phagocytic activity during neurodegenerative conditions, precede Purkinje Cell (PC) death in a Niemann-Pick Type C disease mouse model. One of these developmental proteins is CLEC7A, a protein transiently expressed in microglia precursors during the early postnatal development of the mouse cerebellum. While CLEC7A is not found in healthy adult resting/homeostatic microglia, during neurodegenerative conditions the expression of this protein is significantly increased in activated microglia. In our lab, we found that in contrast to wild-type (WT) mice, NPC1 mutant mice had an increased number of CLEC7A-expressing microglia precursors. Additionally, the expression of the CLEC7A protein was significantly increased at postnatal stages (P10 and P14) where CLEC7A was already decreased in WT mice. Recently, we have been using mice expressing EGFP under the TMEM119 promoter to determine the temporal and spatial development and maturation of CLEC7A^{+} precursors during the postnatal development of the cerebellum. TMEM119 is a microglia-specific protein expressed by mature and homeostatic microglia and significantly decreased in neurodegenerative-associated microglia. The development of the cerebellum occurs postnatally, therefore at P1 age, few IBA1^{+} cells with low levels of TMEM119-EGFP were found in the primitive WT cerebella; no CLEC7A^{+} cells were found at this stage. However, at P4, few CLEC7A^{+} cells were detected in the WT cerebellar. In P7 WT mice, CLEC7A-expressing microglia precursors were abundant with minimal or no expression of TMEM119-EGFP in the developing white matter regions (WMR). Microglia migrating away from the WMR CLEC7A+ clusters had low levels of CLEC7A and higher levels of TMEM119-EGFP. CLEC7A microglia precursors have been associated with phagocytosis of oligodendrocytes precursors. The few CLEC7A^{+} precursors found in the P4 WT cerebellum, coincided with a lack of myelination at this stage as assessed by myelin basic protein (MBP) immunoreactivity. However, strong MBP immunoreactivity was found at sites where CLEC7A^{+} cells were found in the P7 WT cerebellum. Next, we will analyze NPC1 deficient mice to determine if the levels of TMEM119-EGFP are altered in developing NPC1 mutant microglia and associated with the early neurodegenerative phenotype that these cells present before the degeneration of PCs.

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Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.23/B29

Topic: A.01. Neurogenesis and Gliogenesis

Title: Deciphering the role of tenascin-n in peripheral spinal motor nerve development

Authors: *C. G. MARCUCCI[1], A. J. LATIMER[2], S. C. KUCENAS[3];
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Abstract: Peripheral motor nerves are an integral component of the nervous system comprised of many diverse cell types. Congenital disorders (like Charcot-Marie-Tooth (CMT) disease), degeneration, and injury can lead to peripheral neuropathies that can severely affect the quality of life of those afflicted. Currently, treatment strategies for these conditions primarily focus on pain management and physical therapy to preserve function and range of motion. If we had a more complete understanding of how peripheral motor nerves are assembled in development, we would be able to design treatment strategies that could facilitate regeneration of damaged nerves. One of the peripheral motor nerve cell types that we know very little about is perineurial glia (PG). PG are CNS-derived glial cells that form the perineurium of peripheral motor nerves, one of the layers critical for blood-nerve-barrier function in the periphery. Our lab has also demonstrated that PG are critical for ventral motor nerve assembly as disruption of PG specification results in aberrant formation of motor nerves. To begin to uncover the mechanisms driving these processes, our lab generated bulk and single-cell transcriptomic data. These datasets revealed that *tenascin-n (tnn)* is one of the highest differentially expressed genes in PG. Tenascins are a family of extracellular matrix glycoproteins known to be critical in many neurodevelopmental processes via their ability to interact with cell-surface receptors on growing neurites. Tenascin protein expression has also been shown to be upregulated in nerve biopsies taken from patients with CMT1, a particular form of CMT. Further, a *tnn* family member, *tnc*, is expressed in perineurial cells of rats, is an important regulator of nerve regeneration, and is involved in motor axon outgrowth in zebrafish. With this knowledge and our RNA-seq data, I hypothesize that *tnn* is vital for ventral motor nerve assembly. I will use CRISPR/Cas9 targeted mutagenesis in zebrafish to establish a novel mutant *tnn* line and use a combination of *in vivo* imaging, antibody staining, and electron microscopy to fully detail the effect of mutating *tnn*. Further, I will investigate the mechanism by which *tnn* exerts its effects by mutating candidate genes encoding proteins that may interact with TNN. The findings from these studies will shed light on fundamental mechanisms governing peripheral motor nerve assembly and will allow us to devise methods to repair and regenerate damaged nerves.

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Poster

PSTR061. Glial Cell Development and Differentiation

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Topic: A.01. Neurogenesis and Gliogenesis

Support: Undergraduate Mini Grant
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Title: Effects of Fibroblast Growth Factor Receptor signaling and dietary treatments on hypothalamic tanycyte development

Authors: J. STAGRAY[1], N. A. ESTEVE[3], A. N. CHISTOSERDOV[2], J. RICHARD[2], P. WALLS[2], A. FAUL[2], G. NORA[2], D. J. ROGERS[2], *K. M. SMITH[4];
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Abstract: Fibroblast Growth Factor Receptor 1 (FGFR1) is a tyrosine kinase receptor and responds to signaling factors like fibroblast growth factors (FGF) and cell adhesion molecules. FGF-21 is a neuroendocrine signal produced by liver cells to modulate feeding behaviors. FGF-21 is involved in lipo-degradation pathways through MAPK, STAT 1/3/5, PLC γ, and PKC, and in suppression of feeding. FGFR1 is highly expressed within a specialized hypothalamus cell type termed tanycytes.
Tanycytes are specialized radial glial like astrocytes that line the 3rd ventricle (3V) region. There are two primary subdivisions of tanycytes: α and β tanycytes. The α tanycytes are distributed along the medial 3V wall, while β tanycytes are distributed in the ventral 3V wall. Both α and β tanycyte cell bodies interact with 3V CSF. α Tanycytes processes extend deep into adjacent hypothalamic nuclei responsible for governing feeding behavior circuitry. β Tanycytes processes directly interact with fenestrated capillaries of the medial eminence (ME) and assist in the transport of endocrine cues.
In adult mice, progeny cells of tanycytes, including hypothalamic nuclei neurons involved in feeding circuits, detach and integrate into the Arcuate Nucleus (ARC). Additionally, Tanycytes have a demonstrated ability to participate in maintaining glucose homeostasis through expression of GLUT proteins. Alterations in potential morphology interactions involving Tanycytes may ultimately govern cellular mechanisms responsible for regulating feeding behavior pathways. Nestin-Cre mediated Fgfr1 inactivation results in altered tanycyte morphologies compared to control littermates in adult mice. We determined if altered process lengths occur at P0. This allows us to determine if this phenotype is arising in the pre-natal or peri-natal hypothalamic developmental stages. FGFR1 KOs β tanycyte process length are found significantly decreased, and they displayed impaired glucose tolerance compared to control littermates after a High Fat Diet (HFD). HFD induces decreased α and β tanycyte morphological radial process length in FGFR1 KOs. Furthermore, in FGFR1 KO mice after HFD treatment, a decrease in 3V SOX2+ stem cells were observed.
Future studies will examine if postnatal neurogenesis is reduced in FGFR1 KO mice. $FGFR_1$ is also able to form hetero dimers with membrane embedded proteins, such as cellular adhesion molecules. We will investigate potential roles of cellular attachments, and cadherin interactions, between FGFR1 molecules in tanycytes.

Disclosures: J. Stagray: None. **N.A. Esteve:** None. **A.N. Chistoserdov:** None. **J. Richard:** None. **P. Walls:** None. **A. Faul:** None. **G. Nora:** None. **D.J. Rogers:** None. **K.M. Smith:** None.

Poster

PSTR061. Glial Cell Development and Differentiation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.25/B31

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH DC007695

Title: Establishment of the astrocyte population in the medial nucleus of the trapezoid body

Authors: *E. M. AMICK[1], D. T. HELLER[1], A. GABBARD[1], M. ELLISMAN[2], G. SPIROU[1]; [1]Med. Engin., Univ. of South Florida, Tampa, FL; [2]Natl. Ctr. for Microscopy and Imaging Res., UCSD, La Jolla, CA

Abstract: Understanding cell population dynamics during early development faces challenges amid brain enlargement, vasculature expansion, and synaptic competition. A focus of particular interest lies in the pivotal gliogenic switch, a critical developmental event wherein radial glial (RG) cells undergo a transformative process, giving rise to astrocyte and oligodendrocyte precursor cells. We aim to elucidate the intricate cellular dynamics underlying these developmental processes and their implications for neural circuit formation. The medial nucleus of the trapezoid body (MNTB) serves as a valuable model for studying neural circuit formation and is emerging as an advantageous framework for examining the progression of glial cell development and their contributions to the maturation of neural circuits. The precise timeline of astrocyte population dynamics in the MNTB lacks a well-established framework, including embryonic populations. Therefore, our study investigates astrocyte population timing and migratory origins in the developing mouse brain. Utilizing our developmental series of serial block-face scanning electron microscopy (EM) image volumes, we established metrics for classifying cell populations in volume EM at neonatal ages. At postnatal day (P)2, we counted a total of 39 astrocytes, 29 oligodendrocytes, 3 microglia, and 71 neurons. We continued our count of astrocytes, oligodendrocytes, microglia, and neurons, respectively, at sequential perinatal ages and report the following percentages: P3 (N = 68): 26% (n = 18), 18% (n = 12), 1% (n = 1), 54% (n = 37); P4 (N = 47): 26% (n = 12), 32% (n = 15), 4% (n = 2), 38% (n = 18); P6 (N = 109): 25% (n = 27), 35% (n = 38), 1% (n = 1), 39% (n = 43). In our previous findings, we observed a notable transition in the neuron-to-glia ratio from a 1:1 ratio at P3 to a 1:1.5 ratio at P6. Based on these numbers, it can be inferred that the switch in the ratio occurs between P3 and P4. Additionally, we are exploring the earliest arrival of astrocytes in the MNTB by examining embryonic ages and utilizing the astrocyte-specific marker, aldehyde dehydrogenase 1 family member L1. To identify sources of astrocyte migration into the MNTB, we employed Nestin, a glial precursor marker, which shows Nestin-positive processes extending from the ventral edge of the brainstem through the MNTB at P0. Preliminary findings suggest astrocytes may migrate along these fibers into the MNTB, analogous to migration along RG fibers in the cortex. Our ongoing investigation focuses on the early population of astrocytes within the MNTB, shedding light on the glia/neuron transition and identifying potential sources of astrocytes at the ventral brainstem surface.

Disclosures: **E.M. Amick:** None. **D.T. Heller:** None. **A. Gabbard:** None. **M. Ellisman:** None. **G. Spirou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); syGlass.

Poster

PSTR061. Glial Cell Development and Differentiation

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Program #/Poster #: PSTR061.26/B32

Topic: A.01. Neurogenesis and Gliogenesis

Title: Structural remodeling of microglial mitochondria across brain regions and developmental stages

Authors: *K. ESPINOZA, A. SCHALER, M. YU, K. MOORE, C. CHAMORRO, L. DE BIASE;
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Abstract: Microglia play essential roles in the CNS by engulfing newborn cells, pruning excess synapses, and secreting trophic and inflammatory factors. The factors regulating microglial functional and morphological shifts during are not fully understood. In peripheral macrophages, mitochondria act as signaling hubs to regulate cell morphology and secretory function in response to changes in the microenvironment. Recent studies in microglia indicate that cell metabolism may similarly shape microglial functional state in different contexts. In this study, we use a combination of transgenic mice and confocal and live imaging approaches to study key features of microglial mitochondria across development and adulthood. To investigate these organelles, we generated mice with GFP-tagged mitochondria in microglia. We analyzed microglial mitochondria in nucleus accumbens (NAc) and ventral tegmental area (VTA), where these cells display striking differences in multiple cell attributes during development and adulthood. At P8, when microglia show very simplified morphology, mitochondrial mass was elevated. In young adult mice, mitochondrial mass was significantly higher in VTA microglia, which also displays less complex process. To probe the dynamic features of both microglia and their mitochondrial networks, we used two-photon imaging in acute brain slices to analyze mitochondrial reorganization during microglial motility and laser injury. Mitochondria in microglia display fission and fusion events during a 20-minute live imaging session. Mitochondria are localized to proximal processes but not to fine filopodia, which display rapid surveillance. Following focal laser lesion, mitochondria are not trafficked to microglial cell processes that extend toward the site of injury, and display little motility, indicating that mitochondria may not play a central role in rapid reorganization of microglial processes. We also investigated mitochondrial responses to an acute inflammatory insult using lipopolysaccharide (LPS). Microglial mitochondrial mass was elevated at 24-hours post LPS administration as revealed by both histology and fluorescence-based cell sorting. Altogether, our data reveal the in vivo structure of microglial mitochondria from postnatal development to adulthood. These data suggest that mitochondrial status and microglial morphological complexity are linked, but that

mitochondria are not required for rapid reorganization of microglial cell processes. Future directions of this study will continue to provide critical insight into how mitochondria regulate key microglial properties during maturation and responses to CNS insults.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.01/B33

Topic: A.07. Developmental Disorders

Support: KAKENHI 23H02668

Title: Abnormal social memory in different mouse models of autism spectrum disorder based on genetic and environmental factors

Authors: ***M. SATO**[1], M. KIMURA[2], Y. MIYAMOTO[2], A. UEDA[2], M. MAKUUCHI[1], T. TAKUMI[3], M. YOSHIOKA[1], Y. OHMURA[1];
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Abstract: Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder characterized by abnormal social communication and repetitive behaviors. Although a genetic contribution to ASD susceptibility is strongly supported, it is also known to be caused by various environmental factors such as exposure to drugs and pathogens. Mice are social animals and prefer contact with conspecifics to inanimate objects. In addition, social memory, which distinguishes between familiar and novel individuals, is thought to involve multiple brain regions including the hippocampus. In this study, we compared social memory in two different ASD mouse models based on genetic and environmental factors, with the aim of elucidating the neural information processing of social memory and the mechanisms of its abnormalities in ASD. The genetic model used was the 15q duplication mouse, in which the frequent 15q11-13 duplication in ASD was mimicked by paternal duplication of a syntenic region of mouse chromosome 7. For the environmental factor-based model, we used a model in which mice were exposed to valproic acid (VPA) during the embryonic period by administration of VPA (600 mg/kg s.c.) to C57BL/6 pregnant mice at 12 days gestation. Social memory was assessed by allowing a subject mouse to explore a 45-cm square arena containing an empty wire cage and a wire cage with a target C57BL/6 mouse at the opposing corners and measuring changes in time spent exploring the target mouse during repeated 5-min sessions. 15q duplication mice showed no significant differences in exploration time from wild-type mice in the first session. However, in the second and third sessions of interaction with the same target mice, they did not show the characteristic decrease in exploration time seen in wild-type mice as an indication of social memory. On the

other hand, the VPA model mice exhibited significantly shorter exploration time than control mice in the first session, and their exploration times remained shorter than those of control mice in the second and third sessions. These findings suggest that the social memory abnormalities observed in these two ASD model mice may arise from distinct social circuit dysfunctions.

Disclosures: **M. Sato:** None. **M. Kimura:** None. **Y. Miyamoto:** None. **A. Ueda:** None. **M. Makuuchi:** None. **T. Takumi:** None. **M. Yoshioka:** None. **Y. Ohmura:** None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.02/B34

Topic: A.07. Developmental Disorders

Support: NIH/NINDS Grant 1R01NS121120

Title: Gait variations in autism spectrum disorder across the lifespan

Authors: *J. SIMPSON[1], J. WANG[1], M. TERZA[1], M. PALMERO[1], D. J. SHIRLEY[1], W. S. MCKINNEY[4,5,6,7], A.-M. ORLANDO[2], R. ROMERO[2], B. KARMAKAR[3], M. W. MOSCONI[4,5,6], Z. WANG[1];
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Abstract: Autism Spectrum Disorder (ASD) is a lifelong condition that demands long-term support, care, and management. Recent epidemiological and clinical evidence has highlighted an elevated risk for early-onset neurodegenerative diseases in ASD, including Parkinsonism, dementia, and stroke, though quantitative research on aging in ASD is severely limited, and age-related changes in neurological functions are not well understood. Gait atypicalities have been implicated in autistic children and are well-known biobehavioral markers that have power for predicting the onset, progression, and prognosis of separate neurodegenerative diseases. Age-related differences in gait kinematics across the life span and into middle adulthood have not been examined in ASD, but may provide key information on brain development and aging in autistic individuals. In this study, we examined associations between aging and gait variations in autistic individuals. Ninety-one autistic individuals ages 4-75 years and 63 age-, sex-, and full-scale IQ matched neurotypical controls completed 3-5 trials of non-constrained walking at the University of Florida, University of Kansas, and University of Texas Southwestern Medical Center. Autistic individuals showed greater gait variability relative to controls across the lifespan, including standard deviations of step width, step length, step time, and knee angle at heel strike. Due to U-shaped gait variations across the wide age range, participants were separated into the Young (age ≤ 35; ASD = 60, Control =51) and Mid-old (age > 35; ASD = 31,

Control =12) groups. For the Young group, greater age was associated with reduced gait variability for controls but not autistic individuals. Alternatively, no age and group main or interactive effects were identified as significant in the Mid-old group. In summary, our study highlighted increased gait variabilities and nonlinear variations of gait in ASD across the lifespan.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: A.07. Developmental Disorders

Support: Danone North America Gut Microbiome, Yogurt and Probiotics Fellowship Grant (E.K.)
University of California President's Pre-Professoriate Fellowship (E.K.)
NIH/NIGMS R35GM124724 (A.H.)

Title: Maternal Limosilactobacillus reuteri rescues social and emotional recognition behavior in an environmental mouse model of autism

Authors: *E. V. KOZLOVA, M. E. DENYS, A. E. BISHAY, A. HSIAO, M. C. CURRAS-COLLAZO;
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Abstract: Introduction: Polybrominated diphenyl ethers (PBDEs) are thyroid disrupting chemicals with adverse neurodevelopmental effects in children. Our group has previously shown that PBDEs produce autism (ASD)-like traits (Kozlova et al. 2022 Arch Tox; PMID: 34687351) in combination with reduced hypothalamic oxytocin expression in developmentally exposed female mice offspring. Limosilactobacillus reuteri (LR) is a beneficial probiotic that can increase oxytocin and thyroid hormones (THs) in other ASD mouse models. Therefore, we hypothesized that LR can ameliorate PBDE-induced deficits in social behavior, oxytocin and thyroid status. Methods: C57BL/6N dams were dosed with a commercial mixture of PBDE congeners, DE-71, at 0.1 mg/kg/d (DE-71), or corn oil vehicle control (VEH/CON) during preconception, gestation and lactation). Dams were gavaged with L. reuteri (LR) ATCC 6475 at 10^8 CFU/mL (gift of Biogaia, Sweden). Cohort 1 pups (C1) received LR via dam until weaning (PND 21). Cohort 2 pups (C2) continued to receive gavage of LR post-weaning, daily, through 6 mo of age. Results: PCR analysis confirmed increased LR gene expression in feces collected from dams receiving LR and their offspring. LR treatment normalized DE-71-induced deficits in social novelty preference (30 min retention) in adult male ($p<.01$) and females ($p<.05$) and long-term social

recognition memory (24 h retention) in adult female in C2 ($p<.001$). LR normalized the DE-71-induced deficits in the ability to distinguish between emotional state of stimulus mice in C2 males ($p<.01$) and females ($p<.05$). In a marble burying test, compared to VEH/CON, DE-71 exposed offspring showed abnormally elevated scores, which were normalized by LR treatment only in C1 females ($p<.05$). Since social behavior involves discrimination between social odors we also investigated the effects of DE-71 and LR treatment on olfactory discrimination ability. LR treatment normalized DE-71 effects compared to VEH/CON: reduced dishabituation from a non-social to social odor 1 and from social odor 1 to 2 in females and habituation to social odor 1 and dishabituation from social odor 1 to 2 (apparent) in males. Ongoing studies are focused on exploring possible mechanisms underlying the benefits provided by maternal and adult LR therapy. Our early data suggest a potential role of changes in 1) plasma OXT in DE-71 male (C1) mice, and 2) maternal THs in pregnant dams. Conclusions: These results suggest that maternal LR treatment during developmental PBDE exposure provides normalization of ASD-like features in DE-71-exposed offspring in a sex-dependent manner.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.04/B36

Topic: A.07. Developmental Disorders

Support: TRIUMPH Initiative Funding

Title: Relationship between amygdalar functional connectivity, sensory functioning and camouflaging behavior in individuals with autism spectrum disorder.

Authors: *N. NURAINI[1], C. APPLING[1], M. J. PRENDERGAST[4], A. SCHUPP[2], P. MALAKER[3], B. FERGUSON[5], D. Q. BEVERSDORF[6];
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Abstract: Autism spectrum disorder (ASD) is characterized by repetitive behaviors and impaired sensory and social communication. Altered functional connectivity (FC) of the amygdala has been suggested to be associated with some of the clinical aspects of ASD, including hypersensitivity and hyposensitivity. To minimize the visibility of their ASD in social situations, individuals with ASD may camouflage (e.g., suppressing repetitive hand movements, forcing eye contact, using learned rules to respond to non-verbal behavior) to mimic neurotypical behavior. We hypothesized that individuals with higher camouflaging scores would have weaker

amygdalar resting FC in brain regions that involve inferring and understanding other people's perspectives, including the superior temporal gyrus. Our study investigated amygdalar FC at rest in twelve youths aged 18 to 26 with ASD. The left and right amygdalae were individually localized in each participant and used as seed points for FC analyses. The degree of correlation of whole brain amygdalar FC with sensory profile and camouflaging scores, as measured by the Adult Sensory Profile and the Camouflaging Autistic Traits Questionnaire (CATQ), respectively, was examined. We found a significant relationship between sensory impairment with FC amygdala ($r = 0.72$, $p < 0.001$;$r = 0.74$, $P < 0.001$, for the left and right amygdala, respectively). Increased sensory impairment was associated with weaker FC between the right cerebellum and left amygdala but greater FC between the precuneus and right amygdala. There is also a significant relationship between camouflaging scores and these connectivities, occipital cortex/left amygdala ($r = 0.71$, $P = 0.001$), middle temporal gyrus/right amygdala ($r = 0.82$, $P<0.001$), and cerebellum/right amygdala ($r = 0.74$, $P < 0.001$). Individuals with higher camouflaging scores showed weaker FC between the occipital cortex and left amygdala, also between middle temporal gyrus, and right amygdala. However, they show greater FC between the cerebellum and right amygdala. These findings indicate that individuals with ASD have heterogeneous FC between the amygdala and regions of the brain that are important for social communication and language, with weaker connectivity in specific amygdalar connections associated with increased ASD hypersensitivity.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.05/B37

Topic: A.07. Developmental Disorders

Support: NIMH (K01MH119540)
Hawk-IDDRC Pilot Grant (P50 HD103556)

Title: The role of neonatal gonadal hormones in sex-specific deficits relevant to Autism Spectrum Disorder

Authors: *E. M. HAGAN[1], P. QUINONES[2], D. PREUSCHL[1], S. FERRI[1];
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Abstract: Social behavior is seen across almost all living species and when these behaviors are disrupted it can result in decreased chances of survival, reproduction, and quality of life. Social deficits are exhibited in neuropsychiatric and neurodevelopmental disorders, and are a core

symptom of autism spectrum disorder (ASD). ASD affects 1 in 36 children and 4 times as many males as females. Within an ASD diagnosis, males are more likely to exhibit social impairments. The mechanism of this robust sex bias is not well understood. Here, we used neonatal injections of gonadal hormones as a novel experimental system to disrupt sex-specific developmental pathways in mice to determine their effects on behaviors relevant to ASD. We found that testosterone administration on the day of birth, which is equivalent to late gestation in humans, induces male-specific deficits in social approach and fear memory. These deficits were only present when the injection was given on the day of birth and not at postnatal day 18. Furthermore, while testosterone injected on the day of birth did cause social and contextual fear conditioning deficits, it did not affect anxiety-like behavior on an elevated zero maze or body weight over development. Administration of D-cycloserine, a NMDAR partial agonist, which has been shown to ameliorate social deficits preclinically, alleviated the testosterone-induced social and fear deficits. Surprisingly, estradiol given on the day of birth led to female specific social deficits. Currently we are investigating the mechanisms of these sex specific vulnerabilities to social and fear deficits. These findings will aid in advancing the current understanding of how the brain is susceptible to social impairments and help identify novel treatment targets.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.06/B38

Topic: A.07. Developmental Disorders

Support: Ontario Brain Institute
Province of Ontario Neurodevelopmental Disorders Network

Title: Peripheral immune phenotype and behavioural symptoms in children with neurodevelopmental disorders

Authors: *S. R. CLEARY[1,7], C. MATTHEWS[2], G. TESKEY[3], S. ASBURY[4], R. SCHACHAR[8], R. NICOLSON[10,11], R. WEKSBERG[9,12,13], E. ANAGNOSTOU[14], D. M. BOWDISH[5], J. A. FOSTER[6,15];
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Abstract: Presently, behavioural features are the primary assessment method used to diagnose neurodevelopmental disorders (NDDs). Heterogenous within-disorder presentations and symptom overlap between disorders complicate this approach. In a clinical setting, this makes it difficult to match people to effective treatments. Identifying biomarkers representing an individual's biology underlying behaviour can stratify people into more homogenous groups, leading to better treatment approaches. Evidence that the immune system contributes to the development and clinical presentation of NDDs is accumulating; however, previous studies have focused primarily on young children with autism spectrum disorders (ASD). This study expands this scope to phenotype peripheral blood mononuclear cells (PBMCs) and immune signalling molecules and maps them to core behavioural symptoms of NDDs in a large transdiagnostic cohort. Typically developing (TD), attention deficit hyperactivity disorder (ADHD), and ASD participants between 6-18 years old were recruited through the Province of Ontario Neurodevelopmental Disorders Network (POND). Participants completed behaviour assessments measuring social communication, hyperactivity, restrictive behaviours, inattention, and anxiety. Blood samples were collected from a subset of participants; plasma and PBMCs were cryopreserved. Plasma and PBMCs were assessed using LEGENDPlex multiplex assays and flow cytometry. Heterogeneous mixture modelling (HMM) was used to cluster participants by behavioural symptoms. Principal component analysis (PCA) and the Kruskal-Wallis test were used for between-group comparisons. 1716 individuals were grouped into six clusters with distinct behavioural phenotypes using HMM. Five of the six clusters included TD and NDD individuals, while only one was NDD specific. To date, inflammatory markers and PBMCs have been analyzed in a subset of participants, with ongoing data collection. Group comparison shows an increased concentration of BDNF, VEGF, and IL-18 in the NDD group compared to the TD group ($p < 0.05$). PCA biplots suggest an inflammatory phenotype unique to NDDs. We also found increased proportions of B cells and CD4+CD8+ T cells as a % of CD45+ cells in the NDD group compared to TD ($p < 0.05$). Ongoing analysis will examine the association of PBMCs and inflammatory markers with behavioural clusters. The behavioural results support a diagnosis-agnostic approach to stratifying individuals into biologically-based subgroups. Determining how inflammatory phenotypes link to behavioural symptoms is vital in deciphering the biological basis of the clinical heterogeneity found in NDDs.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.07/B39

Topic: A.07. Developmental Disorders

Support: NIH/NINDS Grant 1R01NS121120

Title: A meta-analysis for exploring dementia-associated cognitive dysfunctions and brain morphological changes in middle-to-old aged autistic adults

Authors: *J. WANG, D. CHRISTENSEN, S. COOMBES, Z. WANG;
The Dept. of Applied Physiol. & Kinesiology, Univ. of Florida, Gainesville, FL

Abstract: A meta-analysis for exploring dementia-associated cognitive dysfunctions and brain morphological changes in middle-to-old aged autistic adults Jingying Wang[1], Stephen A. Coombes[1], Zheng Wang[1*1] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL 32611-8205, USA
Cognitive dysfunctions are repeatedly manifested in autism spectrum disorder (ASD) early in life, although rarely systematically explored in middle-to-old aged (>35 years) autistic adults. Several cognitive challenges are evident in autistic children and young adults, mirroring those seen in individuals with dementia. This raises the question of whether being already 'cognitively ancient' during early development would reduce prospects of further cognitive decline or put autistic adults at greater risk for developing dementia. This systematic review aimed to address two questions: 1) Do middle-to-old aged autistic adults exhibit cognitive deficits commonly observed in dementia patients? and 2) Do middle-to-old aged autistic adults show brain structural atypicalities in regions implicated in dementia? To this end, we summarized empirical studies focused on dementia-related cognitive impairments and brain morphological changes in middle-to-old aged autistic adults. Articles involving global cognitive ability, executive function, memory, visuospatial skills, attention, and perceptual speed were reviewed. Brain structural imaging studies were assessed, including T1-weighted MRI, diffusion MRI, PET, and CT. The literature search was conducted in PubMed, EMBASE, PsycINFO, and Web of Sciences, covering peer-reviewed articles from Jan 1, 1980, to Feb 28, 2023. Articles were screened and data were extracted by two independent reviewers. Meta-analysis was conducted following standardized procedures. Autistic adults showed impairments in executive function and short- and long-term memory retention relative to controls. Autistic adults also showed greater hippocampal volume reductions that were associated with visual and working memory reductions. Additionally, lower mean diffusivity in the left corticospinal tract and lower axial diffusivity in the bilateral inferior longitudinal fasciculus were related to elevated executive dysfunction in ASD. Together, our results highlight dementia-related cognitive deficits and brain changes in middle-to-old autistic adults. Consistent with the recent epidemiological studies, we propose that middle-to-old autistic adults may be at a higher risk for developing dementia relative to controls. Further research is warranted to examine dementia-specific biomarkers in autistic adults.

Disclosures: J. Wang: None. **D. Christensen:** None. **S. Coombes:** None. **Z. Wang:** None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.08/Web Only

Topic: A.07. Developmental Disorders

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Title: The transgenerational effect of maternal adverse childhood experiences on offspring neuropsychological development

Authors: *C. CHEN[1], R. OKUBO[2], S. OKAWA[3], S. NAKAGAWA[1], T. TABUCHI[4];
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Abstract: The transgenerational effects of adverse childhood experiences (ACE) have gained attention in recent research, but the mechanisms remain unclear, and there is a lack of evidence from Asia. In this study, we examined the impact of maternal ACE on the neuro-psychological development of the offspring and the involvement of postpartum depression and mother-to-infant bonding difficulties in this effect. We conducted a nationwide internet survey in 2021 and collected data from 5688 postpartum mothers. This study was approved by the ethics committee of Osaka International Cancer Center and written informed consent was obtained from all subjects. We investigated the ACE of the mothers, such as abuse and bullying, and asked them to fill out the Edinburgh Postnatal Depression Scale and Mother-to-Infant Bonding Scale. We also investigated any history of physical and neuro-psychological developmental problems in the child as pointed out by a doctor. The geographical distribution of our subjects across prefectures matches the distribution of women aged 20-49 nationwide. The results showed that the more ACE a mother had, the more likely her child was to have neuro-psychological developmental problems, confirming the transgenerational impact of ACE. Furthermore, this impact was fully mediated by the mother's postpartum depression and bonding difficulties. To prevent and eliminate the transgenerational effects of a mother's ACE, it is crucial to prevent, detect early, and treat postpartum depression and mother-to-infant bonding difficulties.

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Poster

PSTR062. Autism: Behavioral Analysis

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.09/B40

Topic: A.07. Developmental Disorders

Support: CIHR FDN-148423

Title: Metformin as a therapy for Phelan-McDermid syndrome and autism spectrum disorder

Authors: *L. MARSAL GARCIA, J.-H. CHOI, I. GANTOIS, N. SONENBERG;
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Abstract: Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder related to defects in the *SHANK3* gene. People with PMS show hypotonia, delayed development and speech, intellectual disability (77%) and autistic-like behaviors (75%). Shank3 plays an important role in synaptic development and brain function, and alterations in it are found in 1-2% of patients with autism spectrum disorder (ASD) and up to 2% present intellectual disability. Furthermore, memory impairments in individuals with PMS have been reported. Until now, most studies on ASD have been carried out in males, but there is an urgent need to include females in these studies to reduce the knowledge gap regarding sex-specific pathophysiological mechanisms and treatment. Therefore, for this study, we used both sexes of *Shank3B*$^{-/-}$, a mouse model with phenotypes relevant to PMS and ASD, to investigate autistic-like behavior and intellectual disability.We have shown increased signaling of MAPK/ERK pathway. An inhibitor of this pathway is metformin, an FDA-approved drug for diabetes. Thus, we have hypothesized that *Shank3B*$^{-/-}$ mice present memory impairment and sex differences, and that metformin could be a potential treatment to rescue its memory deterioration and autistic-like behaviors.To analyze this, we are performing a battery of behavioral tests in male and female *Shank3B*$^{-/-}$ mice for autistic-like behavior (repetitive behavior, anxiety, and social behaviors), learning and memory (novel object location, novel object recognition, Morris water maze, etc.), locomotion (rotarod and open field), and communication (highly affected in both PMS and ASD; ultrasonic vocalizations). We have some results showing deficits of different types of memory between *Shank3B*$^{-/-}$ male and female mice and its improvement with metformin treatment, and also a rescue of the repetitive behavior in *Shank3B*$^{-/-}$ male mice.We are further looking into *Shank3B*$^{-/-}$ mice from a molecular perspective: we have collected tissue from the main brain regions associated with ASD and memory (prefrontal cortex, striatum, hippocampus, and cerebellum) from male and female *Shank3B*$^{-/-}$ mice and their controls. We are studying total and phosphorylated proteins from the mTOR and MAPK/ERK pathways, and synaptic proteins, using Western blotting. And we are also studying levels of several mRNAs through quantitative reverse transcription-polymerase chain reaction (qRT-PCR).Together, this project is the first that will specifically determine what type of behaviors and signaling pathways are impaired in both male and female *Shank3B*$^{-/-}$ mice, and give us very important insides for targeted treatments for PMS.

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Poster

PSTR062. Autism: Behavioral Analysis

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.10/B41

Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH112734

Title: Developmental trajectory of visual feedback utilization and visual motor memory in autism spectrum disorder

Authors: *A. J. DRIGGERS[1], R. SHAFER[1], J. BARTOLOTTI[1,3], E. BOJANEK[4], Z. WANG[5], M. W. MOSCONI[1,2];
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Abstract: Autistic individuals show atypical sensorimotor development that is associated with clinical outcomes, though sensory and motor control processes contributing to these differences remain unknown. The present confirmatory study in humans aims to clarify the contributions of visual feedback processing and visuomotor memory to sensorimotor development in autism. Fifty-four autistic individuals (16 female) and 34 age-matched controls without autism (19 female), aged 10-35 years, completed tests of precision gripping with and without visual feedback. Participants pressed on force sensors with their index finger and thumb and received visual feedback in the form of a horizontal bar (force bar) that moved upwards with increased force. They were instructed to press so that the force bar reached the level of a static “target bar”, and to hold it as steadily as possible. During ‘Vision’ trials, both bars remained present for the duration of 15s trials. For ‘No Vision’ trials, the force bar was removed after 3s, and participants were instructed to keep their force output at the target level. To assess visual feedback contributions to motor behavior, group and age were included as predictors in linear mixed effects models of force accuracy, variability (coefficient of variance), and regularity (sample entropy). To assess motor memory contributions to behavior, linear regression of the latency, slope, and magnitude of force decay were examined during last 12 sec of No Vision trials. Autistic individuals showed greater age-related increases in force accuracy than controls in the Vision condition only (t_{116}=2.95, p<0.01) and a greater age-related decrease in force regularity ($t_{83.4}$=2.07, p=0.04) and variability across conditions ($t_{85.7}$=-2.35, p=0.02). Decay slope, latency, and magnitude showed no group effects. Pearson correlations showed that autism severity was associated with lower force accuracy (r_{Vision}=-.36, p=0.01) and greater force variability (r_{Vision}=.34, p=.02; $r_{NoVision}$=.29, p=.05) and regularity (r_{Vision}=-.29, p=.05). Our findings suggest that autistic individuals’ ability to integrate visual feedback information to support precision motor behaviors shows a protracted developmental course. Results indicating visuomotor impairments are related to the severity of autism traits implicates overlapping mechanisms, or that early emerging sensorimotor impairments may contribute to core autism features.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.11/B42

Topic: A.07. Developmental Disorders

Support: McPherson ERI: Kenzi Valentyn Grant

Title: The Effects of Dual-Task Interference on Gait in Autistic and Non-Autistic Young Adults

Authors: ***R. W. NELSON**[1], K. A. PICKETT[2], B. G. TRAVERS[3], A. H. MASON[2]; [1]Dept. of Kinesiology, Univ. of Wisconsin, Madison, Madison, WI; [2]Univ. of Wisconsin - Madison, Madison, WI; [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: ***Introduction:*** Previous literature has suggested that adults experience significant motor performance decline when simultaneously performing two motor tasks, such as walking while carrying an object. Furthermore, increases in task complexity are found to differentially affect motor skill performance in autistic individuals when compared to neurotypical individuals. The purpose of this study was to extend the research on complex motor skill development in autism spectrum disorder (ASD) using a real-world dual task. We measured the effects of dual-task interference in neurotypical and autistic young adults, in four different walking and bimanual carrying tasks, ranging from simple to complex. We wanted to determine how parameters of gait were impacted by the increased complexity of the secondary task, and how dual-task effects on gait differed between groups. ***Methods:*** Sixteen non-autistic (10 male, M = 24.55 ± 1.2 years) and fourteen autistic young adults (5 male, M = 23.53 ± 0.7 years) participated in this study. Participants were asked to walk across a Zeno Walkway ™ (4.87m) while performing ten trials in each of four motor tasks: A) simple, overground walking (baseline), B) walking while carrying an empty tray, C) walking while carrying a tray with unstacked wooden blocks, and D) walking while carrying a tray with stacked wooden blocks. We quantified and normalized by leg length spatiotemporal gait parameters of step length (cm), stride width (cm), velocity (cm/s), cadence (steps/min), and also measured the percentage of time in double-limb support (PDLS, %). ***Results:*** Significant main effects of increased task complexity were found for our autistic group in step length, velocity, PDLS, and cadence ($p < 0.001$). Significant pairwise differences between all conditions, except between B and C, were found for velocity ($M_A = 116.31$, $M_D = 84.38$, $p < 0.01$) and PDLS ($M_A = 26.56$, $M_D = 32.05$, $p < 0.05$). Moreover, significant group differences were found for both mean velocity and PDLS ($p < 0.05$), with a significant group x condition interaction occurring in mean velocity and cadence ($p < 0.05$). This interaction indicated that the difference between the autistic and neurotypical participants was larger in condition D than in A for both velocity and cadence, with lower velocity and cadence in the autistic group. ***Conclusions:*** Increasing the complexity of a secondary task performed while

walking results in a more conservative gait in autistic young adults, who also experience greater dual-task effects than neurotypical young adults. These findings provide a better understanding of the motor adaptations made by autistic individuals while performing a walking-and-carrying task.

Disclosures: R.W. Nelson: None. **K.A. Pickett:** None. **B.G. Travers:** None. **A.H. Mason:** None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.12/B43

Topic: A.07. Developmental Disorders

Title: A data-driven resting state parcellation of the whole brain in individuals with autism spectrum disorder

Authors: *J. SHAO, A. PERSICHETTI, S. J. GOTTS, A. MARTIN;
Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Neuroimaging studies of individuals with autism spectrum disorder (ASD) have consistently reported atypical organization in both cerebral cortex and subcortical structures, especially within networks involved in communication and social processing. Despite the wealth of literature documenting atypical brain function and connectivity associated with ASD, a whole-brain functional parcellation in ASD individuals is notably absent. Our goal was to use patterns of resting-state functional connectivity to obtain a whole-brain parcellation in individuals with ASD and contrast it with a functional parcellation in matched typically developing (TD) individuals. We analyzed high-quality resting-state fMRI data (8 minutes 10 seconds) collected from 70 high-functioning ASD individuals (14 female) and 70 TD individuals (19 female). The groups were matched on age, IQ, head motion, and temporal signal-to-noise ratio (tSNR). We first parcellated the cortex (cerebral cortex and cerebellum) by calculating the functional connectivity between voxels within the cortex and all voxels outside of the cortex. We then thresholded the resultant correlation matrices and clustered the group-average matrices using the Infomap algorithm. We required parcels to replicate across 10 randomized split-half samples of the data (35 participants in each half per group). This procedure was repeated for the subcortex (forebrain and brainstem) and the two parcellations were combined and remapped onto the whole brain. We further compared our ASD and TD parcellations using the eta^2 coefficient, a measure of similarity between the parcels. We found three main group differences: First, the parcellation resulted in 78 distinct functional regions in the ASD group compared to 83 in the TD group. Second, the average pairwise eta^2 coefficient across parcels was significantly weaker in the ASD group compared to the TD group. Third, we found significant differences in the parcellations between the groups in the cortex, subcortex, and cerebellum. Our results provide a functional

atlas of the differences between the whole-brain parcellation in ASD compared to matched TD individuals.

Disclosures: **J. Shao:** None. **A. Persichetti:** None. **S.J. Gotts:** None. **A. Martin:** None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.13/B44

Topic: A.07. Developmental Disorders

Support: AS-IA-111-L01

Title: Sex bias in social deficits, neural circuits and nutrient demand inCttnbp2autism models

Authors: *T.-L. YEN;
Academia Sinica, Taipei, Taiwan

Abstract: Autism spectrum disorders caused by both genetic and environmental factors are strongly male-biased neuropsychiatric conditions. However, the mechanism underlying the sex bias of autism spectrum disorders remains elusive. Here, we use a mouse model in which the autism-linked gene Cttnbp2 is mutated to explore the potential mechanism underlying the autism sex bias.Autism-like features of Cttnbp2 mutant mice were assessed via behavioural assays. C-FOS staining identified sex-biased brain regions critical to social interaction, with their roles and connectivity then validated by chemogenetic manipulation. Proteomic and bioinformatic analyses established sex-biased molecular deficits at synapses, prompting our hypothesis that male-biased nutrient demand magnifies Cttnbp2 deficiency. Accordingly, intakes of branched-chain amino acids (BCAA) and zinc were experimentally altered to assess their effect on autism-like behaviours.Both deletion and autism-linked mutation of Cttnbp2 result in male-biased social deficits. Seven brain regions, including the infralimbic area of the medial prefrontal cortex (ILA), exhibit reduced neural activity in male mutant mice but not in females upon social stimulation. ILA activation by chemogenetic manipulation is sufficient to activate four of those brain regions susceptible to Cttnbp2 deficiency and consequently to ameliorate social deficits in male mice, implying an ILA-regulated neural circuit is critical to male-biased social deficits. Proteomics analysis reveals male-specific downregulated proteins (including SHANK2 and PSD-95, two synaptic zinc-binding proteins) and female-specific upregulated proteins (including RRAGC) linked to neuropsychiatric disorders, which are likely relevant to male-biased deficits and a female protective effect observed in Cttnbp2 mutant mice. Notably, RRAGC is an upstream regulator of mTOR that senses BCAA, suggesting that mTOR exerts a beneficial effect on females. Indeed, increased BCAA intake activates the mTOR pathway and rescues neuronal responses and social behaviours of male Cttnbp2 mutant mice. Moreover, mutant males exhibit greatly increased zinc demand to display normal social behaviours.Mice carrying an autism-linked Cttnbp2 mutation exhibit male-biased social deficits linked to specific brain regions,

differential synaptic proteomes and higher demand for BCAA and zinc. We postulate that lower demand for zinc and BCAA are relevant to the female protective effect. Our study reveals a mechanism underlying sex-biased social defects and also suggests a potential therapeutic approach for autism spectrum disorders.

Disclosures: T. Yen: None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.14/B45

Topic: A.07. Developmental Disorders

Support: Simons Foundation Human Cognitive and Behavioral Science Award 874568

Title: Using video games inspired by rodent operant tasks to study evidence accumulation in autism

Authors: *S. CHAKRAVARTY, Y. LI, Q. H. DO, V. TORRES-LACARRA, H. B. TAGER-FLUSBERG, J. T. MCGUIRE, B. B. SCOTT;
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Abstract: Atypical responses to sensory stimuli are common in autism, yet a mechanistic explanation is not clear. Previous studies suggest a deficit in perceptual integration—the process by which sensory evidence is integrated over time—which results in slower response times and reduced accuracy for perceptual decisions, particularly for noisy or ambiguous stimuli. However, previous paradigms have relied on explicit verbal instructions, and included relatively small samples of high functioning autistic participants. Thus, characterization of deficits across the autism spectrum remains to be understood. Here, we examined perceptual decisions with a nonverbal feedback-driven paradigm modeled after pulse-based evidence accumulation tasks used with rodents. Adapting the paradigm into an online video game, we collected data remotely from 179 adolescents (11 to 17 years) across the autism spectrum and 74 age-matched controls. Our sample included 30 minimally verbal autistic participants, who have been largely absent from related studies. 81% of the autistic and 94% of the control participants finished the task and performed above chance level. Autistic participants showed reduced average accuracy ($p<0.05$), reduced initial rate of learning, and reduced slope for the psychometric curve, when compared to the non-autistic controls. Participants Vineland-3 scores, a standardized assessment of adaptive behavior in autism, were positively correlated with their task accuracy and psychometric slope, suggesting greater perceptual deficits for minimally verbal participants. Using a signal detection framework to model individual perceptual decisions as a function of the strength of the evidence, sensory noise, and participant's choice biases, we found that for both autistic and control participants, sensory noise scaled non-linearly with the strength of the evidence. In summary, the

framework we developed can be used to collect meaningful perceptual decision-making data from across the autism spectrum remotely with an online video game and can readily support comparisons with genetic animal models of autism in future studies. Our results extend previous findings on altered sensory processing in autism to a larger, more heterogeneous sample.

Disclosures: S. Chakravarty: None. **Y. Li:** None. **Q.H. Do:** None. **V. Torres-Lacarra:** None. **H.B. Tager-Flusberg:** None. **J.T. McGuire:** None. **B.B. Scott:** None.

Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.15/B46

Topic: A.07. Developmental Disorders

Support: NSF Grant1640909

Title: Ai plus stochastic motor assessments of neurodivergent individuals

Authors: C. L. MCKEEVER[1], K. DOCTOR[6], D. WU[2], A. PHADNIS[3], M. H. PLAWECKI[4], J. I. NURNBERGER JR.[5], *J. JOSE[2];
[1]Physics, [2]Indiana Univ., Bloomington, IN; [3]Med. Sch., [5]Psychiatry, [4]Indiana Univ., Indianapolis, IN; [6]Computer Sci., Univ. of Massachusetts, Amherst, MA

Abstract: We have measured several kinematic variables, using high-definition motor sensors, from a set of 90 individuals with neurodivergent (ND) and typically developing (TD) conditions, while carrying out the reaching paradigm. This included 17, autism spectrum disorder (ASD), 15, attention deficit hyperactive disorder (ADHD), 26 comorbid ASD+ADHD, plus 33 TD. We first analyzed the raw motor data, using AI Deep Learning (DL) techniques. We separated different training sets from unseen confirmation testing sets. During training we have a competition of five different conditions. We found that each one of the unseen conditions were diagnosed with a high precision. To further assess the validity of the diagnostic results we calculated the area under the curve (AUC) from the one-vs-rest Receiver Operating Characteristic (ROC) curves. The AUC shows high values between 72.12% and 96.26% proving that the trained models possess good discriminatory diagnostic ability. Next, we filtered the electronic noise form the kinematic data, identifying millisecond peak fluctuations in the rotational and linear kinematic variables. To characterizes the magnitude changes in the peak fluctuations, which are unique to each subject, we evaluated the probability distribution function (PDF) of the nearest-neighbor max-min oscillations of the rotational and linear kinematic variable's peaks. We characterized the PDFs by the ratio of the variance to the mean, known as the Fano factor. To further measure the amount of millisecond motor randomness present in the movements pertaining to each subject. We also calculated the corresponding Shannon entropy associated to each PDF. This provides information about the amount of randomness, or loss of certainty, present in the movement control from each subject. The DL analyses can identify each

ND condition while the statistical analysis provides an assessment of the severity of the condition. Both approaches can be used in conjunction with clinical tools to develop appropriate therapies.

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Poster

PSTR062. Autism: Behavioral Analysis

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.16/B47

Topic: A.07. Developmental Disorders

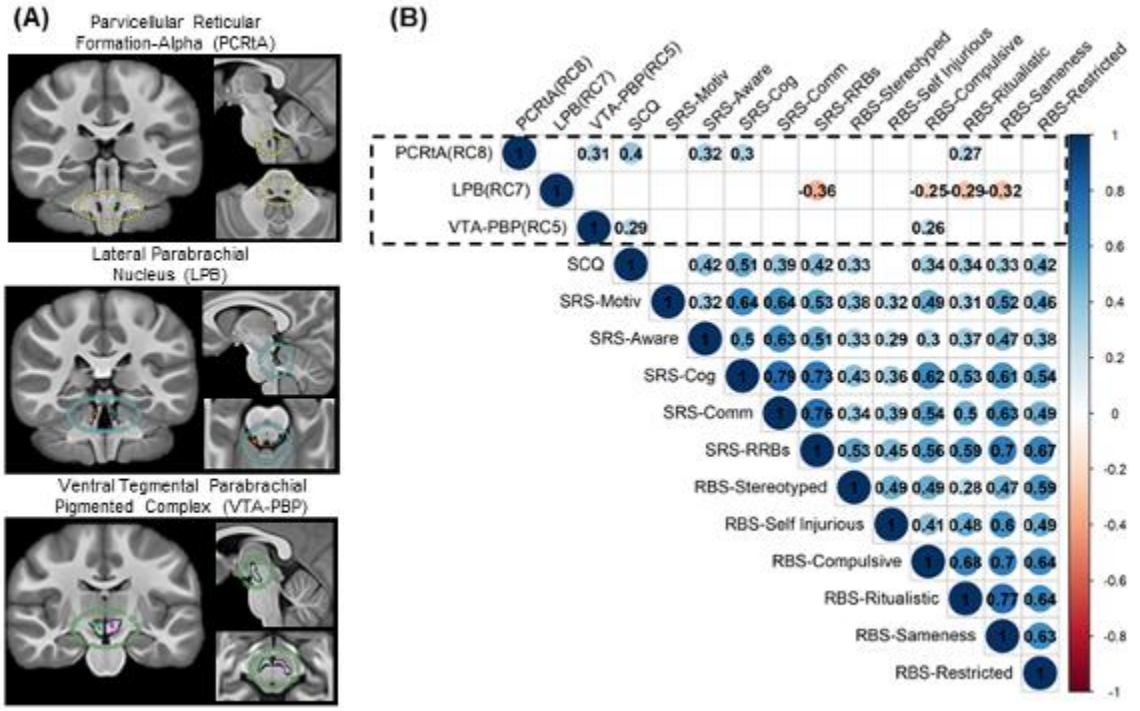
Support: Hartwell Foundation's Individual Biomedical Award
NIH P50 HD105353
NIH U54 HD090256
NIH R01 HD094715

Title: Role of Autonomic, Nociceptive, and Limbic Brainstem Nuclei in Core Autism Features

Authors: *B. TRAVERS[1], O. SURGENT[2], J. GUERRERO-GONZALEZ[2], D. C. DEAN[3], G. R. KIRK[2], N. ADLURU[2], S. KECSKEMETI[2], A. ALEXANDER[4], E. SKALETSKI[2], E. SKALETSKI[2], S. NAIK[5];
[1]Kinesiology, [3]Pediatrics, [4]Wisconsin Natl. Primate Res. Ctr., [2]Univ. of Wisconsin-Madison, Madison, WI; [5]Univ. of Wisconsin - Madison, Madison, WI

Abstract: Although the first biology-based theory of autism posited that the brainstem's reticular formation corresponded to autistic behaviors (Rimland et al., 1964), we still know little about the brainstem's role in autism. This study examined autonomic, nociceptive, and limbic brainstem nuclei in relation to core autism features. In a sample of 71 non-autistic and 74 autistic children (6.0-10.9 years), autism features were assessed using caregiver-reported measures of social communication and repetitive and/or restricted behaviors. Participants completed T1- and diffusion-weighted imaging with acquisition and post-processing techniques aimed to improve brainstem images (Guerrero-Gonzalez et al., 2022). Data reduction of autism features and microstructural measures of 22 brainstem nuclei (Singh et al., 2022) was performed via principal component analyses. Correlational analyses examined associations among autism features and brainstem cluster values. Follow-up analyses examined correlations with specific autism measures. Independent replication was performed in a sample of adolescents (24 autistic, 21 non-autistic; 13.0-17.9 years). Results found that microstructure of the parvicellular reticular formation-alpha (PCRtA), lateral parabrachial nucleus (LPB), and ventral tegmental parabrachial pigmented complex (VTA-PBP) was associated with autism features ($P<.05$, FDR corrected; A), such that the PCRtA primarily corresponded to social communication and the LPB primarily corresponded to insistence on sameness ($P<.05$, FDR corrected; B). The PCRtA and LPB

associations were independently found in the replication sample, but the VTA-PBP was not. These findings suggest that individual differences in pontine reticular formation nuclei contribute to the prominence of autistic features.



Disclosures: **B. Travers:** None. **O. Surgent:** None. **J. Guerrero-Gonzalez:** None. **D.C. Dean:** None. **G.R. Kirk:** None. **N. Adluru:** None. **S. Kecskemeti:** None. **A. Alexander:** Other; ImgGyd, LLC, inseRT MRI. **E. Skaletski:** None. **E. Skaletski:** None. **S. Naik:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.01/B48

Topic: A.08. Development of Neural Systems

Support: NIDCD DC019554
NIDCD DC017489

Title: Genetic profiling of extraocular motor neuron subtypes to identify strabismus-related genes in the larval zebrafish

Authors: ***K. R. HAMLING**, D. GOLDBLATT, P. LEARY, B. ROSTI, G. XIANG, H. GELNAW, D. SCHOPPIK;

Otolaryngology, Neurosci. & Physiology, and the Neurosci. Inst., New York Univ., New York, NY

Abstract: In vertebrates, eye movements are controlled by six eye muscles that are innervated by distinct pools of extraocular motor neurons. Congenital strabismus, a disorder that results in eye misalignment, can arise from genetic mutations that disrupt the differentiation or motor targeting of one or more sub-pools of extraocular motor neurons. While the developmental transcription factor cascade that broadly specifies extraocular motor neurons is known, specific genetic programs that distinguish subtypes is largely unknown. We used RNA sequencing to identify genes that are differentially expressed within extraocular motor neuron pools in the larval zebrafish. Previous work established that motor neuron functional subtypes are topographically organized, and that this organization is related to neuronal birthdate. We combined optical birthdating with bulk RNA sequencing to compare gene expression between pools of early or late-born motor neurons from cranial nuclei nIII/nIV. Analysis identified 1236 differentially expressed genes, with 725 higher in early-born and 511 higher in late-born neurons. Using fluorescent *in-situ* hybridization, we evaluated the spatial expression of 34 candidate genes such as transcription factors, axon guidance molecules, and cytoskeletal proteins. Using this approach, we identified genes that were previously unknown to label spatially distinct populations of motor neurons. To further confirm candidate genes, we used plate-based single-cell sequencing of nIII/nIV motor neurons. From 84 extraocular motor neurons, we observed variable gene expression that identified many of the same candidate genes as bulk sequencing experiments. Using PCA, neurons could be clustered based on gene expression into 3 groups. *In situ*s for highly variable transcripts confirmed that clusters corresponded with topographic location. Finally, we aim to identify a role for candidate genes in ocular motor neuron development using CRISPR-Cas9 mutagenesis. A loss-of-function mutation in the transcription factor *phox2a* – a gene known to cause CFEOM Type II incomitant strabismus when mutated in human patients – caused loss of nIII/nIV motor neurons and resulted in temporal deflection of the eyes, consistent with previous literature. Our work has identified gene markers that are differentially expressed across motor neuron subtypes and validated the zebrafish as a model for testing genetic perturbations to oculomotor development. Future work will further test the functional role of candidate genes in extraocular motor neuron differentiation, axonal targeting, and eye movements to identify putative genes involved in motor disorders of the eye.

Disclosures: K.R. Hamling: None. **D. Goldblatt:** None. **P. Leary:** None. **B. Rosti:** None. **G. Xiang:** None. **H. Gelnaw:** None. **D. Schoppik:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.02/B49

Topic: A.08. Development of Neural Systems

Support: NIH Grant GM129679
Wooten Grant

Title: Decreased Complex N-Glycans Inhibit Neural Tube Formation and Motor Response in Zebrafish

Authors: *C. HATCHETT, R. SCHWALBE, K. HALL;
Biochem. and Mol. Biol., Brody Sch. of Med. East Carolina Univ., Greenville, NC

Abstract: Title: Decreased Complex N-Glycans Inhibit Neural Tube Formation and Motor Response in ZebrafishAuthors: Cody J. Hatchett, M. Kristen Hall, and Ruth A. SchwalbeAbstract The absence of complex and hybrid types of N-glycans in mice is embryonically lethal due to maldevelopment of the neural tube. N-Acetylglucosaminyltransferase-I (Mgat1) catalyzes a required step for converting oligomannose N-glycans to hybrid and complex N-glycans. Zebrafish have two genes (Mgat1a/b) that encode for N-acetylglucosaminyltransferases (GnT-Ia/Ib). Herein, we silenced the Mgat1b gene to determine whether increased and decreased levels of oligomannose and complex types of N-glycans, respectively, would result in disruption of neural tube development and behavior in zebrafish. MALDI-TOF MS verified that the Mgat1b (-/-) strain had higher levels of Man5 oligomannose and lower levels of complex N-glycans in brain relative to Wt AB, verifying that GnT-Ib is silenced. Lectin blotting also showed raised levels of oligomannose in brain and spinal cord. Survivability studies showed that about 40% of the embryos carrying silenced Mgat1b die at 12 hpf and another ~15% by 24 hpf, indicating that neural keel formation is disrupted in most of the dead embryos. Surviving Mgat1b (-/-) embryos (2 and 3 dpf) were less apt to respond to touch compared to Wt AB. In comparing larvae of Mgat1b (-/-) to those of Wt AB, swimming locomotor activity was reduced from 5 dpf to 29 dpf. Currently, we are exploring the expression levels of Mgat1a and 1b in brain and spinal cord of Wt AB and Mgat1b (-/-) strains. Developmental stages of neural tube development which results in embryo death are being further explored, along with the penetrance. Thus, our results support that raised and lowered levels of oligomannose and complex types of N-glycans, respectively, cause maldevelopment of the neural tube, and furthermore surviving embryos and larvae have hampered responses and movement.

Disclosures: C. Hatchett: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH GM129679. **R. Schwalbe:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH GM129679, Wooten Grant. **K. Hall:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH GM129679.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.03/B50

Topic: A.08. Development of Neural Systems

Support: MOST111-2326-B-A49-002
NSTC111-2326-B-A49-001-MY3

Title: Nolz-1 cell lineages constitute a population of mPFC-projecting dopamine neurons in the VTA that modulates aversive behavior

Authors: S.-Y. CHEN, ***F.-C. LIU**;
Inst. of Neurosci., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Progenitor cells in the ventral midbrain give rise to different populations of dopamine neurons. Dopamine neurons in the ventral tegmental area (VTA) constitute the mesocorticolimbic pathways that regulate limbic function, whereas dopamine neurons in the substantia nigra pars compacta (SNc) form the mesostriatal pathway that controls movement. A key question is how dopamine neuron subtypes are specified for distinct neurological functions. Here, we report that the cell lineage expressing the Nolz-1 / Znf503 gene comprises a population of VTA dopamine neurons that preferentially innervate the medial prefrontal cortex (mPFC) that modulates aversive behavior. Nolz-1, a transcription regulator, was co-expressed with Otx2 in progenitor cells of the midbrain primordia. Genetic deletion of Nolz-1 decreased Otx2, a key transcription factor for the specification of VTA dopamine neurons. Conversely, Nolz-1 overexpression increased Otx2. Molecular characterization by chromatin immunoprecipitation and reporter gene assays indicated that Otx2 was a target gene for Nolz-1. Intriguingly, Nolz-1 deletion concomitantly increased SNc-enriched gene expression in VTA dopamine neurons, suggesting de-repression of SNc-enriched genes in the absence of Nolz-1. De-repressed SNc genes in turn may cause aberrant electrophysiological properties, as Nolz-1 deletion rendered VTA dopamine neurons exhibiting SNc-like physiological characteristics. At the circuit level, deletion of Nolz-1 resulted in impaired VTA-mPFC and Nolz-1 knockout mice exhibited abnormality in conditioned place aversion task. Collectively, our study suggests that Nolz-1 not only promotes cell differentiation and axonal connectivity, but also concomitantly suppresses SNc-enriched genes in VTA dopamine neurons. The dual action of Nolz-1 developmental control in promoting VTA but repressing SNc genetic programs enables rigorous specification of VTA cell identity for wiring the VTA-mPFC circuit to regulate aversive behavior.

Disclosures: S. Chen: None. **F. Liu:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.04/B51

Topic: A.08. Development of Neural Systems

Support: NINDS award #R01 NS115881-01A1

Title: The impact of the environment on the development of the motor and somatosensory cortex: How can a dynamic environment influence cortical structure and function?

Authors: *F. GOMEZ[1], M. ENGLUND[3], L. A. KRUBITZER[2];
[1]Psychology, [2]UC Davis, Davis, CA; [3]Neurona Therapeut., Univ. of California Davis, South San Francisco, CA

Abstract: Early experience tunes neural systems to match an organism's environmental context, allowing the organism to generate adaptive behavior necessary for survival, growth, and reproduction in a dynamic environment. Environmental enrichment (EE) studies have shown the potential to illuminate how early-life experiences impact adult behavior by influencing the structure and function of the brain. However, some limitations of these studies are that they are highly controlled and static in nature. In fact, very little is known about neural and behavioral development in the context of complex, highly variable natural environments, the very environments nervous systems have evolved to adapt to and navigate. Furthermore, few studies examine how differences in motor opportunities (affordances) impact motor system development. Thus, the current research aims to measure the influence of a dynamic environment with numerous affordances on the organization of the primary motor (M1) and somatosensory (S1) cortices and motor behavior. Specifically, we are interested in determining whether rearing in a semi-naturalistic environment with diverse movement opportunities can lead to quicker motor development, increased coordination of the limbs, and a more extensive and synergistic (multilimb) body representation in M1 and S1. We do this by rearing Norwegian brown rats (*Rattus norvegicus*) either in standard laboratory housing conditions or in a dynamic semi-natural environment 3000 times the size of standard laboratory cages and quantifying changes in the functional organization of M1/S1 and subsequent motor behavior across development into adulthood. We employ a battery of behavioral tasks designed to investigate differences in limb coordination, gross motor activity, latency in learning, and the ability to adapt to a novel challenge. Furthermore, by utilizing the deep learning algorithm, DeepLabCut, we can extract kinematics from video recordings of the tasks to better compare limb coordination, the emergence of limb utility, and movement strategies. To assess differences in M1/S1 organization, we generated movement maps of the body representations in M1 and S1 with long-train intracortical microstimulation at critical developmental time points (Post Natal Day 28, 40, and $\geq$ 60) and compare cortical real estate devoted to the representation of particular body movements, synergies, and the number of unique synergies, the emergence of these representations, and stimulation thresholds. Results from this study will allow us to appreciate the extent to which rearing experience impacts the development of the motor system and behavioral outcomes.

Disclosures: F. Gomez: None. **M. Englund:** None. **L.A. Krubitzer:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.05/B52

Topic: A.08. Development of Neural Systems

Support: JSPS KAKENHI (21H00440)

Title: Transition of neural activities during the development of Half Center Modeled swimming CPG in Ciona intestinalis type A

Authors: *M. K. UTSUMI[1], Y. TOMINA[2], H. MIKAMI[2], K. OKA[1,3,4,5], K. HOTTA[1];
[1]Keio Univ., Tokyo, Japan; [2]Hokkaido Univ., Hokkaido, Japan; [3]Kitasato Univ., Tokyo, Japan; [4]Waseda Univ., Tokyo, Japan; [5]Kaohsiung Med. Univ., Kaohsiung, Taiwan

Abstract: According to the Half Center Model (Brown, 1911), Central Pattern Generator (CPG) of vertebrates are constituted by motor neurons (MNs), interneurons (INs), and ascending contralateral inhibitory neurons (ACINs). However, it is yet unclear how the neural activities of these components are developed during their embryogenesis. Our previous study revealed that in *Ciona intestinalis* type A, an ascidian model organism with a simple neural circuit, a single pair of MNs (MN2L/MN2R) are determining its spontaneous tail flicking behavior (developmental stage St.22-24) (Akahoshi *et al.*, 2021). MN2s are considered to be one of the main components of *Ciona* CPG, though the neural activities of MN2s during its swimming behavior (St.25-) were not yet investigated. In this study, we investigated the neural activities of MN2s during its later stages and how they are contributed to *Ciona*'s swimming CPG. Long-term simultaneous calcium imaging of MN2s with GCaMP6s/f (St.22-34) revealed that their activities could be classified into 7 Phases (Phase I-VII), depending on the interval and synchronicity of MN2L and MN2R calcium transients. At first each MN2 oscillate sporadically (Phase I, St.22-), and as they develop to swimming larva MN2s gradually oscillate at a constant interval (Phase II-IV, St.24-), synchronize (Phase V, St.27-), oscillate at longer interval (Phase VI, St.28-) and becomes sporadic again after its tail absorption (Phase VII, St.31-). Interestingly, 76% of the embryos started to oscillate from MN2R. Optogenetic experiments by hChR2 revealed that each MN2 directly stimulates its ipsilateral tail muscles (Utsumi *et al.*, 2023). These results indicated that MN2s are a key factor of *Ciona*'s motor rhythm CPG from the tailbud stages, swimming larva, and up to tail absorption stages. Furthermore, contralateral axons of ACIN1s elongated between IV and V, whereas those of ACIN2s elongated between V and VI. An optogenetic approach with hChR2/miniSOG2 (Utsumi *et al*., 2022) suggested that both ACIN1 and ACIN2 are essential for the generation and modification of post-Phase V rhythmic swimming behavior, respectively. Moreover, simultaneous membrane potential imaging of contralateral and ipsilateral MN2/ACIN during swimming behavior directly supported the Half Center Model by reflecting alternate left-right spike timing.

Disclosures: M.K. Utsumi: None. **Y. Tomina:** None. **H. Mikami:** None. **K. Oka:** None. **K. Hotta:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.06/B53

Topic: A.08. Development of Neural Systems

Support: LR20C070002

Title: Developmental features of lower motor neurons in mouse spinal cord

Authors: *H. HUIJIE[1], G. LIANG[2];
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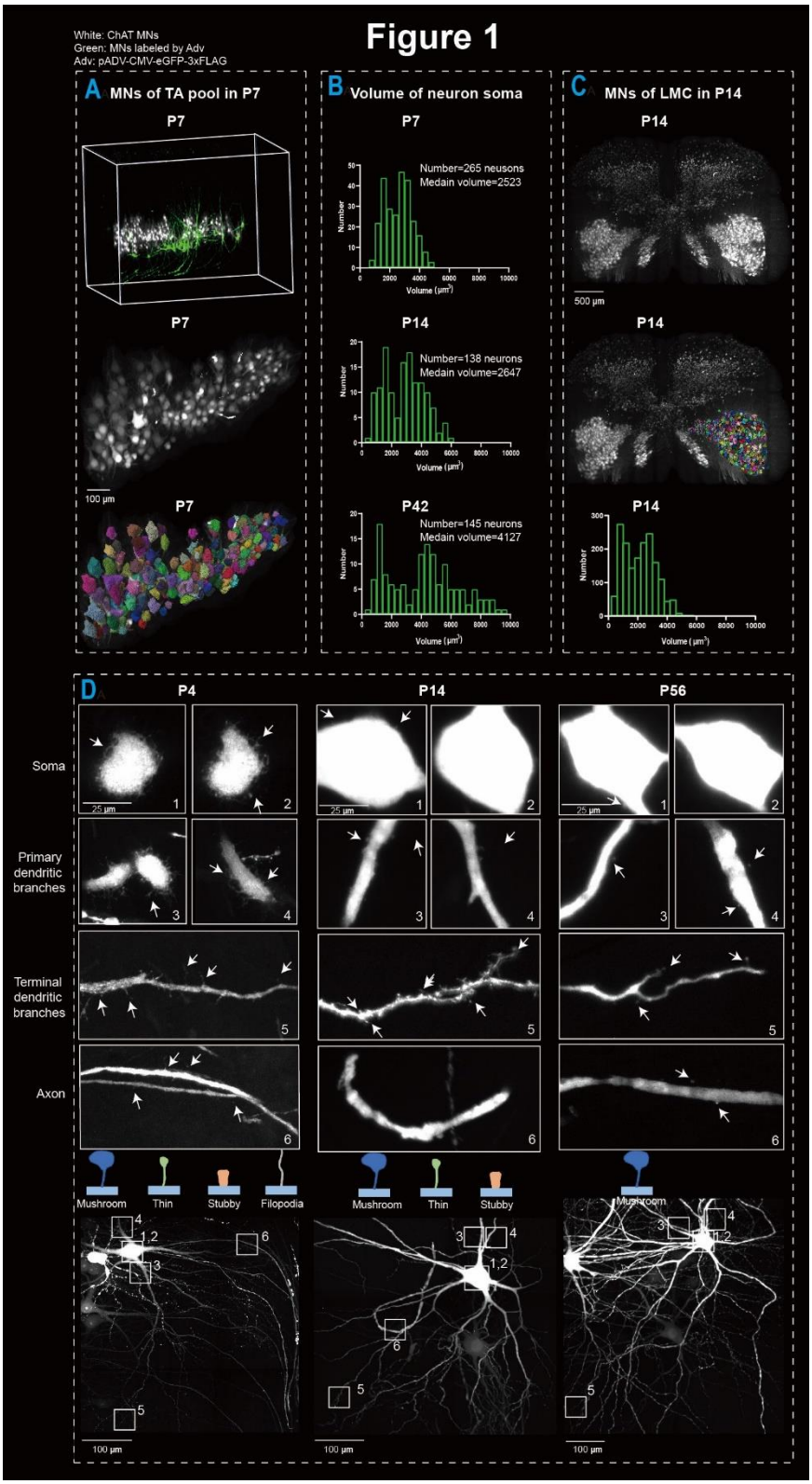
Abstract: The spinal cord motor neurons (MNs) undergo significant changes during its development, but there is few quantitative information regarding the morphological structure of individual MNs. We use a combination of tissue clearing, tissue expansion, Adenovirus (Adv) injection, and tiling light sheet microscopy to explore these problems. We image one motor neuron pool, innervated the Tibialis anterior (TA) muscle, in ChAT-tdTomato mice from P7 to P42, with the MNs sparsely labeled via Adv injection (Figure 1 A, B). We segment the imaged MNs and analyze the soma volume. The results show that the soma volume median of P7, P14 and P42 is 2523, 2647 and 4127 μm^3, respectively. The number of segmented MNs of P7, P14 and P42 is 265, 138 and 145, respectively. There is a clear segregation of two MNs groups in sizes in P42 mice. In addition, we segment the MNs of lateral motor column (LMC) from the spinal cord L3-L5 in P14 mice (Figure 1 C). The volume distribution and median of LMC MNs are similar to MNs of TA pool in P14 mice, suggest that MNs segregation happens gradually with the mice growth. MNs segregate to the α-MNs and γ-MNs. MNs are not fully differentiated at P7 and P14. However, we can distinguish α-MNs and γ-MNs by soma volume at P42. We image the variations of dendritic spines of different ages to understand the ability of MNs to respond to different stimuli. We image the same MNs column in mice of different ages (P4, P14 and P56) via Adv injection (Figure 1 D). Spines are classified as filopodia, thin, stubby, or mushroom spines. We can see the total number of spines are decreased. The types of spines are mainly filopodia and thin in P4 mice. The density of spines is the highest in soma and primary dendrite. The density has a reduction in the soma and primary dendrite in P14 mice. Spines are predominantly mushroom-shaped in P56 mice. These results suggest that young MNs have high synaptic plasticity. However, matured MNs have more limited abilities to learn and change. Together, we make progress in understanding the structure, development of MNs. These features can reveal more about the differentiation and motor control of MNs.



Disclosures: H. huijie: None. **G. Liang:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.07/B54

Topic: A.08. Development of Neural Systems

Support: NIH Grant NS124240-01A1
NIH Grant R01NS114510

Title: Coordinated Expression of Hox5 Transcription Factors Drives Respiratory Circuit Assembly

Authors: *M. T. MOORE, A. VAGNOZZI, M. LIN, E. BROZOST, P. PHILIPPIDOU; Neurosciences, Case Western Reserve Univ., Cleveland, NY

Abstract: Breathing is an essential motor function for terrestrial life. Disrupted breathing due to impaired respiratory neural circuit development is often a fatal symptom of developmental and genetic disorders such as sudden infant death syndrome (SIDS) and Rett syndrome. While diaphragm muscle contractions, the driving force for inspiration in mammals, are controlled solely by motor neurons (MNs) located in the phrenic motor column, complex neural circuitry in the hindbrain regulates respiration. These circuits converge onto the rostral Ventral Respiratory Group (rVRG), which contains the majority of phrenic-targeting neurons. Despite the critical importance of these circuits, the molecular mechanisms that underlie their connectivity are largely unknown. Our lab has previously demonstrated that Hox5 transcription factors (TFs) regulate phrenic MN specification and connectivity. Here, I investigate whether Hox5 TFs similarly drive rVRG development and integration into the respiratory circuit. I identify a novel molecular marker for the rVRG, Cadherin 9, and show that Hox5 proteins are expressed in the rVRG, but not in more rostral respiratory nuclei. Thus, Hox5 TFs may act to confer rVRG-specific characteristics required for connectivity. Dbx1::Cre-mediated conditional deletion of Hox5 TFs from phrenic-targeting premotor populations disrupts inspiratory signal transduction and breathing behavior, resulting in perinatal death. Further, I identify Hox5-dependent pathways acting in medullary phrenic-targeting populations. Thus, I hypothesize that Hox5 TFs, present in both respiratory motor and premotor populations, coordinate respiratory circuit assembly during development.

Disclosures: M.T. Moore: None. **A. Vagnozzi:** None. **M. Lin:** None. **E. Brozost:** None. **P. Philippidou:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.08/B55

Topic: A.08. Development of Neural Systems

Support: Fondation Jean-Jacques et Felicia Lopez-Loreta pour l'Excellence Académique
NIH Pioneer Award DP1 NSI06665
Allen Frontiers Group
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Travis Roy Foundation
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MSTP T32GM007753

Title: Subcellular molecular machinery of corticospinal growth cones is dynamically regulated across developmental stages and locally implements formation of corticospinal circuitry

Authors: *A. ENGMANN, **M. A. VICENT**, P. NANDA, O. DURAK, D. NGUYEN, J. D. MACKLIS;
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Abstract: Corticospinal neurons (CSN) are central for fine motor control. Their cell bodies are located in layer V of neocortex. During development, CSN extend their axonal projections over remarkably long distances to the brainstem and spinal cord, generating exquisitely precise functional circuitry. Injury or degeneration of CSN circuitry causes critical and irreversible loss of motor function in spinal cord injury or ALS/motor neuron diseases.
Over the past two decades, deep investigation of neuronal subtype-specific soma transcriptomes has provided substantial insight into the “molecular logic” of CSN subtype specification, development, and diversity through early-mid corticogenesis. However, knowledge of molecular mechanisms controlling later aspects of development - such as CSN axon elongation, grey matter innervation, branching and collateralization, synapse formation, and functional circuit maturation - is still quite limited. Recent work has revealed that neurons contain multiple distinct subcellular transcriptomes, and that local protein synthesis of axonally-enriched transcripts is required for directional responses to at least some guidance cues, and for formation of presynaptic terminals. However, the composition of subtype-specific GC-localized molecular machinery and the dynamic regulation of these subcellular processes across distinct stages of circuit formation are essentially unknown.
We apply a combination of neuronal subtype-specific labeling, biochemical fractionation, and fluorescent small particle sorting to purify CSN-specific GCs and corresponding parent somata directly from the mouse brain. We investigate subcellular CSN transcriptomes across distinct stages of circuit formation in the first postnatal week in mice. Subcellular mapping of transcripts, as well as analysis of differential changes in the composition of subcellular transcriptomes across stages of circuit development, identifies subsets of GC-localized transcripts and potential regulatory mechanisms for RNA trafficking, stability, and local translation, crucial for the formation of CSN circuitry.
Increasingly deep knowledge of molecular processes that enable successful and specific CSN circuit development promises to also deepen understanding of mechanisms of degeneration or

failed regeneration following injury, and to potentially lead to discovery of new therapeutic approaches.

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

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.09/B56

Topic: A.08. Development of Neural Systems

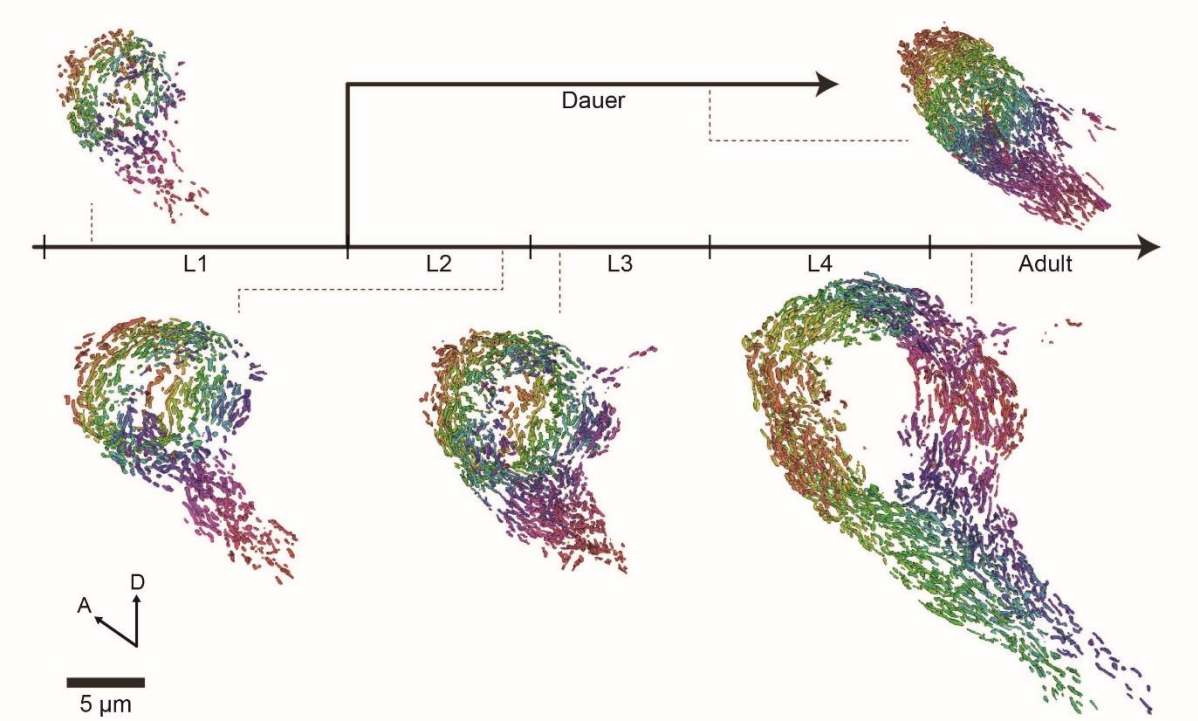
Support: Samsung Science and Technology Foundation SSTF-BA1501-52
NRF Korea 2019R1A6A1A10073437

Title: Comparative study on mitochondrial structure in the neuromuscular system across development

Authors: ***J. A. BAE**[1], M.-K. CHOI[1], S. AHN[1], G. KO[1], H. YIM[1], D. T. CHOE[1], K. C. NGUYEN[2], H. M. KANG[1], S.-K. BAHN[3], D. H. HALL[2], J. S. KIM[4], J. LEE[1];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Albert Einstein Col. of Med., Bronx, NY; [3]Korea Brain Res. Inst., Daegu, Korea, Republic of; [4]Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Mitochondria are highly dynamic organelles that can alter their shape and position according to the needs such as synaptic transmission. Previously, there have been active studies on mitochondrial structure in neurons or muscles. However, prior research has neither examined mitochondria structure within an entire neuromuscular system nor explored its changes across development. Using 3D electron microscopy (EM), we developed semi-automated methods for reconstructing mitochondria in *C. elegans* EM images using deep learning. Consequently, we collected mitochondria reconstructions of normal reproductive stages and dauer, enabling comparative study on morphology and spatial arrangement of mitochondria in different stages. As previous reports, we have validated spatial distribution of mitochondria in neurons is related to the spatial distribution of presynaptic sites. By inspecting the motor neurons, it has been revealed mitochondria adjacent to the postsynaptic sites are longer than mitochondria near the presynaptic sites, consistent with previous findings in mammalian cortical neurons. As motor neurons innervate muscles, we further explored how mitochondrial structure affects the behavior. While it is normal to exhibit high turning rate when *C. elegans* is placed away from the food, we discovered the turning rate significantly decreases in *drp-1* mutants, where mitochondrial structure is disrupted. To test this is due to specific motor neurons, we showed neuron-specific rescue of SMD neurons recovered the normal behavior. Moreover, we discovered stage-specific properties of mitochondrial structure as well. We discovered the size of the mitochondria in neuronal cells of the dauer stage are larger, especially in motor neurons and interneurons regulating head and neck movement. We also found mitochondria in dauer body wall muscles

exhibit unique stranded network structure. We believe these deviations in mitochondrial morphology observed from *C. elegans* dauer could be due to dauer-specific characteristics.



Disclosures: **J.A. Bae:** None. **M. Choi:** None. **S. Ahn:** None. **G. Ko:** None. **H. Yim:** None. **D.T. Choe:** None. **K.C. Nguyen:** None. **H.M. Kang:** None. **S. Bahn:** None. **D.H. Hall:** None. **J.S. Kim:** None. **J. Lee:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.10/B57

Topic: A.08. Development of Neural Systems

Support: NIH/NINDS RO1NS117390

Title: Activation of the sphingosine 1 phosphate receptor 1 restores blood-brain barrier integrity and function in intraventricular hemorrhage

Authors: *A. MISHRA[1], B. CHENG[2], D. SHARMA[2], K. SCHAEFFER[3], T. HLA[4], P. BALLABH[2];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]ALBERT EINSTEIN COLLEGE OF MEDICINE, Bronx, NY; [3]Jacobi Hosp., Bronx, NY; [4]Harvard Med. Sch., Boston, MA

Abstract: Intraventricular hemorrhage (IVH) is a major neurological complication of prematurity which often results in cerebral palsy, cognitive impairments, and hydrocephalus. IVH can disrupt the integrity and function of the blood-brain barrier (BBB), allowing myeloid cells to infiltrate the brain, and fluids to exude, thus worsening the consequences of IVH. Sphingosine 1 phosphate (S1P) is a key regulator of the BBB, which mediates through the activation of G-protein coupled receptors (S1PR1-5). S1PR1 stabilizes the BBB by regulating adherens and tight junction functions, limits leukocyte infiltration, and inhibits astrogliosis. We hypothesized that the occurrence of IVH would disrupt adherens and tight junctions, increase BBB permeability, and exacerbate inflammation in premature newborns with IVH. In addition, S1PR1 activation might restore interendothelial junctions, ameliorate inflammation, and reduce BBB permeability in IVH. Our well-established rabbit model of IVH (E29 kits) was employed to test these hypotheses. Adenoviral delivery of S1PR1 (Ad-S1PR1) into the cerebral ventricles was used to upregulate S1PR1 expression in kits with IVH. Interendothelial molecules were quantified by Western blot analyses. We found that IVH reduced the expression of tight junction molecules, including occludin at postnatal day (D) 3 and claudin 5 at D7. However, VE-cadherin was comparable between kits with IVH and without IVH. S1PR1 expression was also reduced in kits with IVH. Injection of tracers, including 2% fluorescein Dextran 10 (10 kD) and 2% Texas red Dextran 3 (3 kD) into the jugular vein showed that the onset of IVH led to the permeability for 3 kD tracers, but not for 10 KD tracer at D3 and D7. Both 3 and 10 kD tracers did not penetrate the BBB in kits without IVH. We next evaluated the effect of Ad-S1PR1 treatment in kits with IVH. The expression of claudin-5, occludin and VE-cadherin was higher in S1PR1-treated kits compared to Ad-GFP controls. Immunohistochemistry and stereological quantification revealed that the number of $CD3^+$, $CD19^+$, and $CD11B^+$ cells was reduced in Ad-S1PR1 treated kits compared to controls. Ad-S1PR1 treatment also reduced the BBB permeability to 3 KD tracers in kits with IVH. The data suggest that the activation of the S1PR1 receptor restores the tight junction molecules, contains inflammation, and minimizes blood-brain permeability in kits with IVH. We speculate that S1PR1 activation might enhance the neurodevelopmental outcome of premature infants with IVH.

Disclosures: **A. Mishra:** None. **B. Cheng:** None. **D. Sharma:** None. **K. Schaeffer:** None. **T. Hla:** None. **P. Ballabh:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.11/B58

Topic: A.08. Development of Neural Systems

Support: NIH Grant PA-18-484

Title: Probing the maturation of extraocular motor neuron subtypes driving gaze stabilization

Authors: *C. BELLEGARDA, P. LEARY, D. SCHOPPIK;
Otolaryngology and Neurosci. & Physiol., New York Univ. Langone Med. Ctr., New York, NY

Abstract: All vertebrates stabilize gaze with a simple circuit that transforms sensed head/body tilts into corrective counter-rotations of the eyes. While gaze stabilization improves as animals mature, the rate-limiting step in circuit development (sensory, motor, or otherwise) remains unknown. To investigate the neuronal constraints on behavior improvement, we measured longitudinal responses of motor neurons innervating the superior oblique (SO) extraocular muscle to body tilts. We found that motor neuron responses acquire directional selectivity and strength between 3 and 5 days post fertilization (dpf), followed by a plateau. As gaze stabilization behavior continues to improve after 5 dpf, a motor neuron response plateau suggested a bottleneck for functional maturation downstream of motor neurons. We assayed neuromuscular junction (NMJ) development in the SO muscle using a label for a postsynaptic acetylcholine receptor subunit (alpha-bungarotoxin). Longitudinal alpha-bungarotoxin labeling revealed a steady increase in the presence and size of extraocular NMJs between 3 and 9 dpf, well-matched to the time course of behavioral improvement. Our findings suggest that development of the motor periphery for eyes-down movement, as specified by the SO muscle, is a bottleneck for the vestibulo-ocular reflex circuit, and as such constrains the ability of developing zebrafish to stabilize gaze. To understand the response properties of all subtypes of extraocular motor neurons, we use a new transgenic line labeling all extraocular motor neurons to probe the timescales of maturation for different motor neuron subtypes. These experiments will reveal if development across the motor neuron pools in the motor periphery share common factors or if distinct characteristics are responsible for different timescales influencing the maturation of behaviors for developing sensorimotor circuits.

Disclosures: C. Bellegarda: None. **P. Leary:** None. **D. Schoppik:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.12/B59

Topic: A.08. Development of Neural Systems

Support: NIH R35GM118183

Title: Investigating effects of neuron size on neural development and function in Xenopus

Authors: *X. LIU, C. WAN, R. HEALD;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Neuron size influences neuronal properties and inter-neuronal interactions, but the effects of neuron size on the development and function of the nervous system is poorly understood. We use *Xenopus*, a powerful model for research in both neural development and biological size control, to study how neuron size impacts neural development *in vivo*. We take

advantage of the observation that cell size generally correlates with genome size and use *Xenopus* embryos of different ploidy to compare the development between nervous systems composed of differently sized neurons. Our flow cytometry and whole brain imaging analyses indicate that neurons of artificially induced triploid tadpoles are ~1.5 times larger than diploid neurons. Interestingly, the increase in neuron size is accompanied by a decrease in neuron number in triploids, resulting in only slightly increased brain size. Consistent with these observations, triploid brains display lower levels of cell proliferation and distinct wiring patterns during development, suggesting a less complex, less flexible brain. Additionally, we found that triploid tadpoles show significantly altered swimming behavior compared to their diploid siblings, indicating functional consequences of physiological changes at the cell level and structural modifications at the brain level due to the increased neuron size. We are currently combining immunofluorescence, flow cytometry, circuit tracing, calcium imaging, and brain-specific RNA-seq to characterize neuron size-dependent changes in brain structure, connectivity, and activity, and to explore the underlying mechanisms. Together, our study signifies the functional importance of neuron size and provides new insights into biological size control during development at multiple levels. This project also deepens our knowledge of the principles and mechanisms of vertebrate neural development.

Disclosures: **X. Liu:** None. **C. Wan:** None. **R. Heald:** None.

Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.13/B60

Topic: A.08. Development of Neural Systems

Support: NIH/NINDS R01NS131662
NTRAIN/NICHD K12HD093427
Swiss National Science Foundation

Title: Molecular specification of cortico-brainstem versus corticospinal projection neurons in development

Authors: ***P. PATEL**[1], J. KAISER[1], F. DÜNDAR[2], J.-P. TETUAN[1], N. ANGIRA[1], E. SIEGER[1], K. CELENTANO[1], V. V. SAHNI[1];
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Abstract: Skilled motor control requires precise connections between subcerebral projection neurons (SCPN) in the cerebral cortex and their appropriate subcerebral targets in the brainstem or spinal cord. The brainstem is an important motor control center and cortical projections to the brainstem serve distinct motor control functions than corticospinal projections. However, mechanisms controlling cortico-brainstem versus corticospinal projections during development

remain unknown. Here, we show that the transition between the brainstem and cervical cord distinguishes cortico-brainstem from corticospinal neurons from the earliest stages of SCPN axon extension in white matter. We used high throughput single-cell RNA sequencing of FACS-purified SCPN, retrogradely labeled from either the cerebral peduncle (labeling both cortico-brainstem and corticospinal neurons) or the cervical cord (labeling corticospinal neurons only) at critical times of axon extension. We identify that cortico-brainstem and corticospinal neurons are molecularly distinct. We establish *Neuropeptide Y* (*Npy*) as specifically enriched in cortico-brainstem neurons in lateral cortex, while *CART prepropeptide* (*Cartpt*) delineates cervical-projecting corticospinal neurons. Our results highlight molecular specification of cortico-brainstem vs. corticospinal projections well before these axons reach their appropriate segmental target and suggest a broad molecular program over SCPN axon targeting to distinct subcerebral targets early in development. These findings are likely to inform future investigations of motor circuit development, as well as approaches aimed at enhancing motor recovery after central nervous system damage.

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Poster

PSTR063. Development and Maturation of Motor Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.14/B61

Topic: A.08. Development of Neural Systems

Support: NIH/NINDS R01NS131662
NTRAIN/NICHD K12HD093427
Craig H. Neilsen Foundation, Award #727694
Wings for Life Spinal Cord Research Foundation

Title: A Gain-of-Function Screen to Identify Novel Genes Driving Coritcospinal Axon Projection Targeting

Authors: *J. T. LUSTIG[1], A. LAMMERS[1], P. PATEL[2], P. NGUYEN[3], J. CONNER[3], E. AZIM[4], V. V. SAHNI[5];
[1]Burke Med. Res. Inst., White Plains, NY; [2]Burke Neurolog. Inst., White Plains, NY; [3]Mol. Biol. Lab., Salk Inst. for Biol. Studies, La Jolla, CA; [4]MNL-E, Salk Inst., La Jolla, CA; [5]Burke Neurolog. Inst., Burke Neurolog. Institute, Weill Cornell Med., White Plains, NY

Abstract: The corticospinal tract (CST) facilitates skilled, precise movements, which necessitates that corticospinal neurons (CSN) establish precise connectivity with spinal circuitry. Recent work has identified CSN-intrinsic molecular determinants that function during development to establish segmentally specific CSN axonal projections to distinct levels of the neuraxis - bulbar-cervical vs. thoraco-lumbar. However, evidence suggests that there are

additional, yet unidentified genes that play similar roles in controlling CSN axon targeting. In the present study, we detail a new strategy to identify novel gene candidates, and investigate their effects on CSN axon projection targeting using gene misexpression. We first establish AAV-mediated gene delivery in newly generated Klhl14-T2A-Cre knock-in reporter mice as an approach to reliably analyze axon targeting by the subset of CSN in lateral cortex that project exclusively to bulbar-cervical levels ($CSN_{BC\text{-}lat}$). We first establish that this strategy identifies known regulators of CSN axon targeting - Crim1 and Cbln1. Using this new approach, we then undertake a gain-of-function screen to investigate gene candidates and identify novel regulators of CSN axon targeting. For several of these regulators, this is the first description identifying their potential roles in regulating axon growth and guidance anywhere in the central nervous system. Our results provide proof-of-concept of a novel approach for *in vivo* testing of candidate gene function in controlling context-appropriate CSN axon guidance in a relatively high-throughput manner.

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

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.01/B62

Topic: A.08. Development of Neural Systems

Support: JSPS KAKENHI JP16H06462
JSPS KAKENHI JP20H00522
JSPS KAKENHI JP22K15204

Title: Repeated neural activations induce long-term structural plasticity of the nucleus

Authors: ***T. MURANO**[1], H. HAGIHARA[1], K. TAKAO[2], K. KATOH[3], M. NAMIHIRA[3], T. MIYAKAWA[1];
[1]Fujita Hlth. Univ., Toyoake, Japan; [2]Res. Ctr. for Idling Brain Science, Univ. of Toyama, Toyama, Japan; [3]Biomed. Res. Institute, AIST, Tsukuba, Japan

Abstract: Activation of neurons induces plastic changes in neural circuits, which are essential for brain development, learning and memory, but their overactivation can lead to pathological changes in the brain. However, in such conditions, what changes in neurons at the cellular level and how they are induced remain unclear. Here, we show that repetition of neural activation can induce global and long-term changes in the nuclear structure of neurons and hyper-locomotor activity in mice. While most changes in the transcriptome and epigenome caused by neural activation repeated for a few days are short-term and reversible, subchronic neural activation stabilizes the altered state for at least two weeks. Furthermore, we found that it induces the expression of cell cycle-related genes and changes in the nuclear structure, which partially

resemble the G2-M phase in cycling cells. These cell cycle-like changes and hyper-locomotor activity in mice were inhibited by the knockout of cyclin B, an essential molecule in the G2-M phase transition. Our results demonstrate that repeated neural activation reinstates a cell cycle-like process in neurons and causes global alterations in nuclear structure, which may lead to chronic changes in neuronal functions and locomotor activity. Our findings provide novel insights into the understanding of activity-dependent plastic changes in neuronal circuits, which may be relevant to the pathogenesis of neuropsychiatric disorders.

Disclosures: **T. Murano:** None. **H. Hagihara:** None. **K. Takao:** None. **K. Katoh:** None. **M. Namihira:** None. **T. Miyakawa:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.02/B63

Topic: A.08. Development of Neural Systems

Support: R00-MH124434
Brain and Behavior Research FDN Young Investigator Award

Title: Impaired social behavior following early life adversity coincides with enhanced neuronal activity and changes in the transcriptional profile of the developing rat BLA

Authors: *C. A. MEDINA[1], D. E. COBB-LEWIS[1], M. SONG[1], E. REGIER[1], P. BENDALE[1], M. OPENDAK[2,1];
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Abstract: Early life adversity (ELA) is a major risk factor for neuropsychiatric diseases such as anxiety and depression. Previous work using the maternal separation (MS) and scarcity-adversity via limited bedding (LB) models of ELA suggest that the long-term behavioral consequences of ELA such as asocial behavior and impaired threat processing coincide with increased c-Fos expression in the basolateral amygdala (BLA) and changes in the transcriptomic profile of the BLA. However, because MS and LB are both social manipulations (i.e., alter maternal care or presence), our lab developed the deconstructed adversity model (DAM-ELA) to disentangle the role of social and nonsocial contexts on the effects of ELA in the pup. This approach also permits us to ensure each pup receives a consistent treatment, as well as distinguish pup stress effects from effects on the dam. Briefly, DAM-ELA involves removing pups from the nest for 90 minutes each day from P8 through P12 and either leaving them alone, repeatedly shocking (0.5 mA tail shock every 5 mins) them alone (nonsocial adversity), or repeatedly shocking them in the presence of an anesthetized lactating dam (social adversity). Importantly, some of the pups (littermates) are left undisturbed in the home cage with the original mom. Using this paradigm, we previously found that social adversity but not nonsocial adversity reared pups exhibit reduced social behavior similar to the LB rearing paradigm during a social approach test at P13. We

hypothesized that changes to the transcriptomic profile and hyperactivity of the BLA in social adversity reared pups underlies these social deficits. To address this hypothesis, we performed RNA-sequencing of the BLA following a maternal social approach test at P13, and in a separate cohort of DAM-ELA pups recorded from the BLA using in-vivo multi-unit recording between P15-17. We found that social adversity produced social deficits at P13 while other treatments spared social behavior and changes in the transcriptomic profile of the BLA. Additionally, we show that the asocial behavior continues thru P45 in social, but not nonsocial adversity-reared pups.

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Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.03/C1

Topic: A.08. Development of Neural Systems

Support: R00-MH124434
Brain and Behavior Research FDN Young Investigator Award

Title: Characterizing the impact of early life adversity on parvalbumin interneurons function in infant social behavior

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Abstract: For altricial species, strong attachments between the caregiver and infant are essential for the immature infant's survival and serves as a template for lifelong social behavior patterns. Despite the importance of forming appropriate attachments in early life, we have limited understanding of the neural circuits supporting attachment, and how these can be perturbed during development to produce immediate and lasting social behavior deficits. Dysregulation of inhibitory signaling has been proposed as a likely mechanism. Indeed, patients with schizophrenia and other disorders characterized by atypical social behavior exhibit a loss of parvalbumin expressing GABAergic interneurons (PV INs), the main interneuron found in the basolateral amygdala (BLA). Likewise, stress during critical periods of development in rodents has been linked with a decrease in PV INs activity. While these studies have helped elucidate our understanding of the function of PV interneurons in the context of social behavior and fear, they have solely focused on the adult brain, leaving our comprehension of their operation in the infant brain limited. This developmental information is critical to understand because of the unique functioning of the infant brain and its heightened vulnerability to early experience. We hypothesize that perturbations early in development impact social behavior in the infant rat and

predict that stimulating BLA PV interneurons is sufficient to rescue behavior deficits. We modeled atypical infant attachment in rats using a low bedding (LB) adversity-rearing protocol. To test our hypothesis, we transduced PN5 PV cre pups with Cre-dependent excitatory DREADDs and reared the pups in control or adversity conditions from PN8-12. Next, the pups underwent social behavior testing with a dam at PN15 (infancy) and age-matched peers at PN22 (juvenile) and PN45 (adolescence) with the DREADD ligand CNO (clozapine-n-oxide, 5mg/kg) onboard to specifically control PV INs during behavioral testing. Extracellular in vivo recordings were performed to validate CNO effects on baseline and stimulus-evoked BLA activity. Following adversity rearing, PN15 pups showed increased time spent behind the mother's back, an atypical behavior. Stimulating hM3dq-transduced PV cells with CNO rescued this social behavior deficit. Additionally, we found that the social behavior deficits in the LB group decreased in adolescence and PV stimulation produced distinct outcomes at this age from those in infancy. Overall, these results suggest a causal role for PV IN dysfunction in social behavior deficits after early adversity.

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Poster

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Support: U2COD023375
U24OD023382
U24OD023319
UH3OD023313
5U2COD023375-06

Title: Relations Between Peripheral Epigenetics and Amygdala Volume in a Healthy Pediatric Population

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[2]SOLS, [1]Arizona State Univ., Phoenix, AZ; [3]Dept. of Radiology, Children's Hosp. Colorado, Aurora, CO; [5]Dept. of Pediatrics, [4]Brown Univ., Providence, RI

Abstract: Background: Brain volume is a key measure of healthy development early in life. Neurodevelopment may be impacted by epigenetic mechanisms such as DNA methylation (DNAm). DNAm has been shown to be impacted by environmental factors such as exposure to stress and early life experiences. Changes in DNAm can impact levels of gene expression that alter brain structure and function. The amygdala, part of the limbic system, plays a crucial role in

regulating emotions and encoding emotional memories. It has become best known for its role in the processing of fear but is also involved in processing positive stimuli as well. This study aimed to assess the DNAm of key stress-modulating genes *NR3C1* and *FKBP5* as well as the serotonin-transporter gene *SLC6A4* in association with bi-lateral amygdala volume in a healthy pediatric population. **Methods:** This study included participants [N = 250; females = 113; age range < 2 months - 14 years, M_{age} = 5.17, SD_{age} = 3.61] from a larger longitudinal study (ECHO). DNA was extracted from participant saliva samples. DNAm was measured on an Illumina EPIC array. Principal components analysis was used to create a DNAm variance score for each candidate gene. FreeSurfer was used to calculate brain volume on T1 images. **Results:** First principal components (PC1) of all three genes predicted bi-lateral amygdala volume with sex, cell-count, and days between scan and genetic collection as covariates [FKBP5 (β = 0.18, p = 0.01); NR3C1 (β = 0.20, p = 0.006); SLC6A4 (β = 0.17, p = 0.017)]. **Conclusions:** These results show that peripheral DNAm may be a predictor of grey matter volume, particularly in the amygdala, and elucidates a potential mechanism by which environmental stressors can influence psychiatric and behavioral outcomes later in life. Future analyses will investigate potential effects of genotype within this relationship.

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Poster

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Topic: A.08. Development of Neural Systems

Support: R00-MH124434
Brain and Behavior Research FDN Young Investigator Award

Title: Worth the risk? Effects of development and early care quality on lateral habenula involvement on infant social behavior flexibility

Authors: ***A. GEORGE**[1], S. HU[1], D. COBB-LEWIS[1], O. NGUYEN-LOPEZ[1], E. TESONE[1], A. SU[1], M. SONG[1], K. PACKARD[1], J. WANG[2], M. OPENDAK[1];
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Abstract: Flexible social behavior is critically important during early life when environmental demands are in constant flux. Yet, heightened circuit plasticity during this period also renders the infant vulnerable to environmental influences that guide lifelong social behavior. However, the circuit mechanisms linking early experience to lasting social behavior patterns remain unclear. Here, we use a rodent model to study the ontogeny of the lateral habenula (LHb), a key negative regulator of dopaminergic signaling, in social behavior in typical and perturbed development. To perturb development, we used the Scarcity-Adversity model of Low Bedding (SAM-LB) from

postnatal (PN) days 8-12, in which the dam is given limited nesting materials. In our first experiment, habenulae were dissected at PN18/PN28 and assayed for levels of CaMKIIβ. In our second experiment, PN18/PN28 rat pups were injected with radiolabeled glucose prior to receiving mild tail shocks or no shocks, alone or with a social partner present. Brains were removed and analyzed with autoradiography. In our third experiment, we bilaterally transduced PN3 pups with the DREADDs receptor hM4Di in the LHb or in medial prefrontal cortex (mPFC) projections to the LHb. To chemogenetically inhibit the LHb or mPFC-LHb, we injected PN18/28 pups with clozapine-N-oxide or saline control prior to peer sociability tests with/without ambient predator odor. In our final experiment, we conducted in-vivo multi-unit LHb recordings in PN18/PN28 control and SAM-LB reared pups. We observed an increase in CaMKIIβ expression in PN28 pups compared to PN18 pups, regardless of rearing condition. The increase in CaMKIIβ, which is expressed in excitatory neurons, suggests greater neural activity. In support of this, metabolic imaging showed that at PN28, social presence and shock (threat) were associated with increased glucose uptake in the LHb. Chemogenetic inhibition of the LHb decreased social approach at PN18 and increased social approach at PN28 when threat odor was present, suggesting a developmental transition. Interestingly, chemogenetic inhibition of the mPFC-LHb projection rescued social approach in SAM-LB reared animals. Together, these data implicate LHb circuitry as a target for early intervention.

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Poster

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JPB Research Network on Toxic Stress: A project of the Center on the Developing Child at Harvard University
Rosamund Stone Zander Translational Neuroscience Center Fellowship

Title: Estimating chronological age from resting EEG power in children aged 2-36 months

Authors: *W. W. AN[1,2], A. C. BHOWMIK[3,4], C. A. NELSON[1,2], C. WILKINSON[1,2]; [1]Developmental Med., Boston Children's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Hofstra Univ., Hempstead, NY; [4]Columbia Univ., New York, NY

Abstract: Disruptions in early brain development are believed to underlie the emergence of neurodevelopmental disorders (NDDs). Establishing a model associating objective brain signals with chronological age can provide insights into potential deviations in the development of young brains and aid in early identification of NDDs. This study uses longitudinal resting state EEG data to develop a computational model capable of accurately estimating age in typically developing infants/toddlers aged 2-36 months old, and then tests whether model estimates are lower than the actual age in infants later diagnosed with autism spectrum disorder (ASD). 938 EEG recordings from 467 TD children were pooled from 4 longitudinal studies, and 72 features from the power spectral density of EEG were extracted using spectral parameterization and principal component analysis. Several regression models were trained using the above features to estimate age in days, and the performance of each model was assessed via a 5-fold cross-validation. We further made a test set with 246 EEGs from 85 children later diagnosed with ASD and 246 age-matched EEGs from TD children. Our best performing model, trained on TD data excluding the ones in the test set, was then applied to the test set, and the prediction accuracy was compared between the two groups. Among models, the multilayer perceptron (MLP) showed the highest performance, achieving an R^2 value of 0.85 and a mean absolute error (MAE) of 87.83 days - only 8% of the age range of the participants (1091 days). MAE for other models ranged from 114.6 to 132.2 [XGBoost (R^2 = 0.75; MAE = 114.6), LASSO (R^2 = 0.70; MAE = 130.0), Random-Forest (R^2 = 0.68; MAE = 132.2)]. Testing of MLP-based predication on the ASD and age-matched TD groups showed comparable age-estimates 2-30 months. Age estimates for 30-36 month-olds showed larger prediction error for ASD compared to TD children ($p = 0.005$) with the model underestimating the age of the ASD group. In summary, the proposed MLP model can effectively capture age-related information from EEG power and make accurate estimation of age. Moreover, it exhibits potential in identifying neurodevelopmental conditions such as autism. These findings underscore the robustness of this computational framework and demonstrate its potential as a valuable benchmark for studying brain development. Significantly, the affordability of EEG and the adaptability of this framework ensure the accessibility of this technology by a diverse population.

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Poster

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Title: Developmental trajectories of EEG aperiodic and periodic power suggest timing of thalamocortical development during infancy

Authors: *C. WILKINSON[1], L. YANKOWITZ[1], J. Y. CHAO[2], R. GUTIERREZ[3], S. SHINNAR[2], P. L. PURDON[4], C. A. NELSON[5];
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Abstract: The developing infant brain undergoes dramatic structural and physiological change over the first three years after birth. In particular, during this period, thalamocortical connections are established through an intricately choreographed sequence that plays a critical role in the developmental of sensory cortical networks. The development of thalamocortical circuitry is notable for transient connections that drive subsequent circuit formation, however the timing of thalamocortical development in humans is largely unknown. Longitudinal resting state EEG can provide repeat measurement of change in synchronized neural network activity that result from developmental brain maturation, including thalamocortical circuitry. In this study we examine longitudinal resting-state EEG data from 592 healthy infants aged 2 to 40 months old (1335 EEGs) to characterize the early developmental trajectories of aperiodic and periodic EEG features. We observe varying rates of age-dependent nonlinear changes that are suggestive of distinct milestones in early brain maturation. Consistent with known increases in brain volume and synaptogenesis, we observe rapid increases in aperiodic offset in the first year, with minimal change between 1 to 3 years. Consistent with the transient developmental progression of thalamocortical circuitry, we observe transient periodic peaks in alpha power at 2-3 months and high beta power at 4-18 months. A low beta peak (12-20Hz) also begins to emerge in some infants starting as early as 6-9 months of age. We hypothesized that developmental changes in beta oscillations reflect maturation of GABAergic interneuron networks and thalamocortical connectivity. Infant anesthesia studies have found that GABA-modulating anesthetics do not induce thalamocortical mediated frontal alpha coherence until 10-12 months of age. Using a small cohort of EEG recordings of infants (7-12 months old) before and during exposure to GABA-modulating sevoflurane anesthesia, we find that those infants with a low beta peak (n = 11) had significantly higher thalamocortical-dependent, anesthesia-induced alpha coherence than those without a low beta peak (n=11; *Ancova with sevo level as covariate* $p < 0.05$). Together, these findings suggest that early age-dependent changes in alpha and beta periodic peaks may reflect timing of thalamocortical network development.

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Poster

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Support: Swiss National Science Foundation (n. 33CM30_140334, n. 32473B_135817/1, n. 324730- 163084, PI PSH)
Dora and the Prim'Enfance Foundations

Title: Preterm infants show an atypical processing of the mother's voice: an EEG study

Authors: *D. BENIS[1,2,3], M. FILIPPA[1,3], A. ADAM-DARQUE[1], P. S. HUPPI[2], D. GRANDJEAN[3];
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Abstract: To understand the consequences of prematurity on language perception it is fundamental to determine how atypical early sensory experience affects brain development. To date the neural oscillatory correlates in the time-frequency domain of voice processing as a function of atypical early sensory experience, as after premature birth, remain elusive.
At term equivalent age, ten preterm and ten full-term newborns underwent high-density EEG recordings during mother or stranger speech presentation, presented in the forward (naturalistic) or backward order.
A general group effect terms > preterms for the naturalistic mother's voice is evident in the theta frequency band in the left temporal area, where only full-term newborns showed an increased activity for the mother's voice, whereas preterm infants showed significant activation for stranger naturalistic speech. Similarly, a significant group contrast in the low and high theta in the right temporal regions indicates higher activations for the stranger's speech in preterms. Finally, only full-term newborns presented a late gamma band increase for the maternal naturalistic speech, indicating a more mature brain response.
The current study based on neural time-frequency patterns, demonstrates that preterm infants lack selective brain responses to mother's naturalistic voice typical for full-term newborns, whereas preterms are selectively responsive to stranger voices in both temporal hemispheres.

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Poster

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Topic: A.08. Development of Neural Systems

Support: CONACYT for the Ph.D. fellowship 823584

Title: Dynamic functional connectivity in preterm and term infants.

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Abstract: The human brain is not a static system; there are fluctuations in brain connectivity, i.e. the dynamics of brain functional connectivity (DFC). In this work, we characterize the DFC in preterm and term infants. We selected 171 preprocessed structural-functional datasets from the developing HCP (Hughes et al., 2017), acquired at term-equivalent age (39-44 weeks of postmenstrual age (PMA)) and with no radiological signs of white matter lesions. Data sets were organized into groups according to their gestational age at scanning (weeks gestation, WG): Preterm (< 28 to 37), Full term (37 to 40) and Post-term (41 to >42). We used the swept window technique to calculate the variability in DFC (59 windows of ∼30 seconds, overlap of 15 seconds), estimating the correlation matrices of the resting (sleeping) state BOLD signal from areas of the neonate AAL atlas (Shi et al., 2011), then they were Fisher's Z transformed. We applied K-means clustering independently for each subject (k=4), then we used those centroids and applied another K-means for each group. Finally, we calculated a global K-means with the centroids from the groups, and the optimal number of clusters was 6 based on the elbow criterion. Each cluster is a connectivity state. Of the six states, there is one that is characteristic for each group, state 3 is characteristic of full term subjects, showing only positive connections; State 2, characteristic of post-terms, shows positive and negative connections. Finally, state 5, characteristic of preterms, positive and negative values are observed, but the negative connections are only concentrated in limbic and temporal regions. The other three states (1, 4 and 6) are common to all three groups, two of these states have only positive correlations with values very close to 0 and the other are positive correlations very close to 1. The time spent between the three common states is similar for the three groups, state 1: premature 26.22%, full term 28.84%, postterm 25.92%, state 4: premature 23.37%, full term 24.35%, postterm 23.58% and state 6: premature 24.29%, full term 23.90%, postterm 23.34%. The highest connections among all states include regions of the occipital, parietal and temporal lobes that support the primary sensory systems, the first to develop during the third trimester of gestation (auditory and visual), which are more sensitive to alterations in premature infants. Hughes et al., (2017) Magnetic Resonance in Medicine, 78(2), Shi et al., (2011), PloS one, 6(4).

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Poster

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Topic: B.07. Network Interactions

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Title: Individualized Functional Brain Networks in Newborn Infants

Authors: *J. MOSER[1], S. KOIRALA[1], T. MADISON[1], R. J. M. HERMOSILLO[1], L. A. MOORE[1], J. T. LUNDQUIST[1], L. HADERA[1], A. K. LABONTE[2], M. C. CAMACHO[2], M. MYERS[2], C. M. SYLVESTER[2], D. A. FAIR[1];
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Abstract: Functional brain organization derived from resting state (rs) fMRI data can be used as an indicator for healthy brain functioning and development and is highly individual specific, which can be demonstrated given sufficient amounts of data. For infant neuroimaging, collecting large amounts of data for individual precision functional mapping poses a challenge. Recent work has investigated Template Matching (TM) as a network mapping technique that only requires relatively few minutes of low-motion data to create highly individual specific networks. However, in a split-half reliability analysis in an infant sample, even with 25 minutes of data network maps did not reach a stable plateau of reliability (quantified by normalized mutual information (NMI)). Using 210 minutes of high quality rs-fMRI data from a neonate (over five consecutive days), we determined the amounts of data needed to reach a stable plateau of reliability of individual networks. We quantified the stability of networks by comparing the various intervals of a split-half of the data to each other and to the half treated as ground truth (100 minutes from 16 runs). Within-subject network similarity plateaued at around 60 minutes of the available 100 minutes of data with an NMI of 0.62. Comparing different non-overlapping 20 minute intervals to the held-out data, NMI values ranged from 0.49-0.59 (M=0.54, STD=0.04) and from 0.40-0.53 when comparing the intervals to each other (M=0.48, STD=0.04). These estimates were considerably more stable than NMI between 10 minute intervals of data and the held-out half (0.36-0.51 (M=0.43, STD=0.05)) or different 10 minute chunks of data (0.25-0.44 (M=0.34, STD=0.05). These results indicate that findings from adolescents and adults where stable individual networks could be detected with 10 minutes of low motion data do not apply to infants and even 20 minute intervals still show considerable variability. Using dedicated multi-day protocols, acquisition of more than 60 minutes of low motion data in individuals is possible for small scale precision imaging studies. For larger scale studies, we propose to account for individual differences by using a probabilistic brain network atlas approach. Probabilistic atlases - indicating areas of high overlap of network assignments across individuals in a group - exist for adolescents and adults: https://midbatlas.io. Omitting areas with high variability of network assignments between individuals will strengthen group level analysis and is an approach that can be combined with precision imaging studies to learn more about the development of functional connectivity networks in the first weeks and months of life.

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Poster

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Topic: A.08. Development of Neural Systems

Support: NSF Grant 1735095

Title: Emergence of synergistic information structures in human infant brains during early maturation

Authors: *T. F. VARLEY[1], O. SPORNS[2], M. MYERS[3], M. G. WELCH[4], S. VANHATALO[5], A. TOKARIEV[6];
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Abstract: The perinatal period of development is characterized by the self-organization of neural activity into a complex system supporting a wide range of cognitive functions. These functions require coordination between multiple different neural systems, and these complex processes can hardly be described by simple pairwise interactions between brain regions [1]. This calls for an approach that can account for higher-order interactions in the brain. In this study we applied the O-information (Ω), a measure of higher-order structure in multidimensional data [2] to cortical signals reconstructed from high-density EEG data of preterm infants (N = 289), to explore the emergence of synergistic (”greater-than-the-sum-of-their-parts”) structures in the brain during early maturation (33-45 weeks). We found that the infant brain goes from a highly redundant structure to a more synergetic one: correlation between Ω and age was ρ ⁢ −0.42, p ⁢ 0.001 (Spearman test). The ”synergetic core” at preterm age (33-36 weeks) is small and predominantly localized to the frontal areas. But at the age of 37-40 weeks (before term), it first recruits occipital system and at the age of 40-43 weeks (after term) it expands also over central and temporal regions. We further found that the degree of synergy, as well as the size of the synergistic core at full-term age correlated to cognitive outcomes (Bayley Scales) assessed at 18 months, suggesting that neural synergy may be an efficient biomarker to predict later cognitive development. Finally, we compared developmental trajectories of Ω between two groups of preterm infants: a) standard care group (SC) vs. b) infants participating in Family Nurture Intervention (FNI) program which was aimed to enhance mother-infant emotional connection [3]. The FNI group showed a steady trend through early maturation: from highly redundant to synergetic structure. At the same time, SC infants showed bi-phasic trajectory: redundancy was slightly increasing until week 38 (”plateau” phase) followed by abrupt changes towards synergetic structure (”steep” phase). After full-term age groups showed no difference. Our results show that starting from the third trimester infant human brain dynamically develops synergetic structure and amount of entropy predicts later neurodevelopment. Moreover, support

of natural mother-infant connection modulates the developmental trajectory of these changes and associates with more gradual reorganization processes in the developing brain.

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[2] Rosas et. al. Phys. Rev. E, 100(3):032305, Sept. 2019.
[3] Welch et. al.. BMC Peds., 13(1):148, Sept. 2013.

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Poster

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Topic: A.08. Development of Neural Systems

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Title: Developing wearable OPM-MEG to assess brain function in infants

Authors: *M. E. EVANS, C. CARRENO, B. HOWELL;
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Abstract: Magnetoencephalography (MEG) is a noninvasive neuroimaging modality with millisecond temporal resolution making it ideal for capturing neuronal activity while still having strong millimeter spatial resolution. Recent innovations in MEG using optically pumped magnetometers (OPM) allow for a wearable system to collect changes in magnetic fields generated by groups of neurons. OPM-MEG has shown to have lifetime compliance, but its application in infant research has yet to be explored, leaving much room for innovation. However, current adult cap designs are not suitable for infant use as they cannot support the weight of rigid caps and flexible caps do not provide the rigidity necessary for robust data collection. Therefore, further development is necessary to optimize caps for infant research. This poster aims to provide evidence regarding the feasibility of OPM-MEG in infants, to explore the adaptations in cap design, and protocols to optimize data collection. Participants included in this study are full term, typically developing infants with no prior birth complications and between the ages of 3 to 8 months. Upon enrollment and consent into the study families take sagittal and frontal pictures of their infant's head used for cap development. The cap can be adjusted to fit the size and shape of each individual's head and is 3D printed using polylactic acid (PLA) prior to their first visit. To ensure minimal cap movement infant's are fitted with a breathable bonnet with fasteners to align with the rigid cap. Second generation QuSpin OPM sensors are secured into the cap, the magnetically shielded room is degaussed, and the nulling coils are engaged. Data is collected using cMEG Acquisition software and sensors are managed through QuSpin. During the testing session, participants are presented with auditory, visual and somatosensory

stimuli consistent with previously tested SQUID tasks. To date we have successfully collected OPM data from 10 sessions and 9 enrolled infants aged 3 to 8 months old. Visual quality control of the data looks promising and data processing will help to provide empirical evidence to support utilizing this neuroimaging modality in infant research. Our findings demonstrate the feasibility of OPM-MEG for infant use as supported by the completion of multiple successful data collection sessions. Adaptations to cap design have been used in order to collect data while still maintaining infant comfort. Continued advancement of this approach shows great promise for the field of neurodevelopment.

Disclosures: M.E. Evans: None. **C. Carreno:** None. **B. Howell:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.13/C11

Topic: A.08. Development of Neural Systems

Support: NIMH, IRP
NIMDS, IRP

Title: Early life cingulate lesions blunt arousal-induced breathing responses

Authors: S. SHEIKHBAHAEI[1], G. NAGARAJAN[2], M. BISHOP[3], *Y. CHUDASAMA[4]; [1]NIH, Bethesda, MD; [2]Section on Behavioral Neurosci., Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [4]NIMH, Bethesda, MD

Abstract: Animal models have revealed that the emergence of the fear response in infants can be linked to developmental changes in amygdala circuitry. Like the amygdala, the cingulate cortex contributes to emotional behaviors and exerts regulation over autonomic responses. Anatomically, the anterior cingulate cortex (ACC) is in a position to influence amygdala response to fear-inducing stimuli through its strong connections. It also receives unidirectional input from the temporal hippocampus, a structure that is also associated with fear and anxiety. Thus, we first asked whether early-life lesions of the ACC alter behavioral responses to fear-inducing stimuli. We used the common marmoset *(Callithrix jaccus)* as our model organism, since this small new world primate is susceptible to a broad range of potential predators and display a wide range of facial and full body reactions when subjected to a fearful situation varying from freezing and predator-specific alarm vocalizations, to defensive-aggressive displays. Behavioral Observation Research Interactive Software (BORIS) was used to categorize behaviors into approach or defensive reactions. We found that adolescent monkeys that had received ACC lesions as neonates (postnatal day 10 - 16, n=4) expressed the same basic defensive reactions as sham controls (n=3) when exposed to the fear-inducing object, a fake owl. Since neurons in the cingulate cortex correlate with various aspects of visceral or autonomic responses in a number of species, the measurement of whole-body plethysmography to assess

breathing functions in these animals when highly aroused provided a useful autonomic index of the fear response. A fear- or non-fear-provoking object was presented outside the Plexiglass plethysmography chamber, in full view of the monkey, as we measured respiratory activities continuously. As expected, control animals experienced an increase in respiratory rate upon appearance of the fear object, but not when presented with a non-fearful neutral object. Those monkeys with early life ACC lesions, however, showed no such elevation in breathing in response to the fearful stimulus. These data can shed light on the important role of the ACC in developmental processes, particularly as it pertains to autonomic control of affective behavior.

Disclosures: S. Sheikhbahaei: None. **G. Nagarajan:** None. **M. Bishop:** None. **Y. Chudasama:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.14/C12

Topic: A.08. Development of Neural Systems

Title: Maternal postnatal depression is associated with older brain age in infants and worse toddler cognitive performance

Authors: *H. SUN[1], D. SCHEINOST[2];
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Abstract: Maternal mental health plays a critical role in the early development of the infant brain, shaping the infant's future temperament, emotionality, and behavioral patterns. Previous research has indicated that maternal depression impacts offspring's brain and cognitive development. However, the effects of maternal health on human infant brain structure and subsequent cognitive outcomes are not fully understood.To address this gap in knowledge, we investigated how infant structural connectivity and future cognition performance are affected by maternal depression with 642 neonates from the developing Human Connectome Project. All neonates were scanned at birth, while 563 mothers completed the Edinburgh Postnatal Depression Scale (EPDS) screening to estimate their depression level. 503 neonates underwent cognitive testing (BSID-III) at 18 months old. Standard DWI preprocessing was performed. Structural connectivity for each subject was constructed with the 90-node infant atlas based on the quantitative anisotropy between any two nodes. We used Connectome-based Predictive Modeling (CPM) to predict the postmenstrual age for each infant based on their brain structural connectome. The difference between actual age and predicted brain ages was further used to understand the relationship among maternal depression, infant brain structure, and cognition performance in a late age. The predicted brain age was significantly correlated with the true postmenstrual age for each infant (Pearson correlation: r=0.80, p=1.45e-142) with a 10-fold cross validation. This predicted brain age represents a potential individualized measure of brain maturation. We found that the more depressed the mother was at birth, the older their baby's

brain was (Pearson correlation between EPDS scores and predicted brain age error: r=-0.15, p=5.56e-4), and that maternal depression level was negatively correlated with infant cognition and language performance at 18 months (cognition: r=-0.052,p=0.044; language: r=-0.13, p=0.0047). Furthermore, the structural connectivity strength of the depression-altered infant brain regions fully mediated the correlation between maternal depression and infant cognition performance and partially mediated the correlation between maternal depression and infant language performance at 18 months old. In summary, our study highlights the importance of maternal depression in promoting optimal brain development and cognitive outcomes in infancy and beyond, emphasizing the need for further research to fully understand the impacts of maternal depression on infant brain structure and cognition performance.

Disclosures: **H. Sun:** A. Employment/Salary (full or part-time):; Yale University. **D. Scheinost:** A. Employment/Salary (full or part-time):; Yale University.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.15/C13

Topic: A.08. Development of Neural Systems

Title: Developmental Changes in the Default Mode Network: Insights from Longitudinal Infant Neuroimaging

Authors: *M. SERAJI[1], ***M. SERAJI**[1], S. ROBILLARD SHULTZ[2], A. IRAJI[1], V. CALHOUN[1];
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Abstract: The default mode network (DMN) is a prominent brain network involved in self-referential thinking, introspection, and memory consolidation. However, little is known about the developmental trajectory of the DMN during early infancy. In this study, we aimed to investigate the spatial changes and temporal dynamics of the DMN in a cohort of 158 infants, scanned longitudinally between the ages of 0-6 months.
Using independent component analysis (ICA), we extracted the DMN from functional magnetic resonance imaging (fMRI) data acquired during each infant's scan. We applied a rigorous quality control procedure to ensure data reliability and included at least one scan per infant, with some infants having up to three scans. By analyzing the DMN across multiple time points, we sought to elucidate the developmental changes in the spatial configuration of the DMN.
Our results revealed intriguing findings regarding the development of the DMN during early infancy. Specifically, we observed an increasing inter-subject similarity between the DMN spatial patterns across time. This finding suggests that the DMN undergoes a maturation process characterized by greater spatial coherence and stability as infants progress through the first six months of life. These findings align with previous research indicating the ongoing development of large-scale brain networks during this critical period.

The observed increase in inter-subject DMN similarity highlights the establishment of a more mature functional architecture underlying self-referential and introspective processes. These developmental changes in the DMN may be linked to the maturation of cognitive functions and the emergence of self-awareness during early infancy. Additionally, our findings contribute to the growing understanding of the ontogeny of large-scale brain networks and their implications for cognitive development.
Overall, this study provides novel insights into the developmental trajectory of the DMN during the first six months of life. The observed increase in spatial similarity suggests the progressive refinement and integration of functional connections within the DMN. These findings contribute to our understanding of the early development of self-related cognitive processes and lay the groundwork for future investigations into the functional significance of the DMN during infancy and beyond.

Disclosures: **M. Seraji:** None. **M. Seraji:** None. **S. Robillard Shultz:** None. **A. Iraji:** None. **V. Calhoun:** None.

Poster

PSTR064. Early Neural Development

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Program #/Poster #: PSTR064.16/C14

Topic: A.08. Development of Neural Systems

Support: NSERC Grant RGPIN-2018-04933
CFI Grant 36876

Title: Influence of Semantic and Perceptual Processing on Reasoning and Memory in Children and Adults

Authors: *A. MCARTHUR, M. L. SCHLICHTING;
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Abstract: Previous work has shown that similarity between items (e.g., perceptual, semantic) can facilitate learning of new associations, but also hinder reasoning when similarities must be ignored. Moreover, there is evidence of both individual and developmental differences in the type of information to which people orient their focus, which may interact with one's ability to reason and remember. In particular, ongoing brain development may lead children to have difficulty inhibiting particular types of information or relational similarities. Here, we sought to determine how a cognitive orientation toward semantic or perceptual information influences the operations involved in suppressing irrelevant but similar distractors to make correct reasoning decisions, as well as encoding new associations. We had children (6-8 years) and adults (18-35 years) first complete an intermixed set of analogy and matching problems, followed by a pair learning task. The reasoning problems were presented using pictures, with analogies in an A:B::C:? format where participants select the option D such that the C:D relation mirrors that of

A:B (Whitaker et al., 2018). On the matching problems, participants were cued to select an image that was either semantically or perceptually similar to a central image. On this task, adults were faster and more accurate than children across trial types, while accuracy was higher overall on matching than analogy problems. We further found that a preceding semantic matching problem both elevated the tendency to erroneously select a semantic lure when cued to match based on perceptual features, and led to faster correct responses among adults on analogy problems. These effects may have arisen due to the preceding problem evoking a cognitive orientation toward semantic information, which may spill over into the subsequent trial and lead people to focus on semantic similarities. Next, for the memory task, participants were presented with image pairs that were either semantically or perceptually similar. After, memory for all pairs was tested in a cued recall format. Both children and adults displayed better memory for semantic than perceptual associates. Across age groups, memory for semantic associates tended to be better when the pairs were preceded by other semantic pairs during learning, again consistent with the idea that orienting toward semantic information can benefit memory. Overall, the findings suggest that orienting toward semantic information has a lingering impact on both reasoning and memory formation. Future fMRI analyses will characterize the influence of perceptual and semantic states on neural operations during these processes.

Disclosures: A. McArthur: None. **M.L. Schlichting:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.17/C15

Topic: A.08. Development of Neural Systems

Title: Investigating the Relationship between Early Life Stress-Induced Behavioral Deficits and Immune Response

Authors: *M. NGUYEN, L. HALLADAY;
Santa Clara Univ., Santa Clara, CA

Abstract: Exposure to trauma during early childhood can incite a variety of lifelong behavioral deficits, including anxiety, depression, and social behavioral disorders. Previous studies have demonstrated a link between stress exposure and immune system deficiencies, but the extent to which early life trauma specifically alters the immune system is not clear. It is well established that early life trauma during critical developmental periods can hyperactivate the body's stress response system, the hypothalamus-pituitary-adrenal (HPA) axis, interfering with maturation of several components of the central nervous system, including the brain and potentially the immune system. Our overall goal is to explore whether there is a common mechanism underlying the psychological and physiological deficits stemming from early-life trauma. To investigate this, using an animal model of early life trauma, we examined whether the severity of behavioral deficits correlated with the extent of wound healing impairment. We employed mouse

maternal separation, an established mouse model of childhood neglect, which we have previously shown to permanently interrupt social motivation and increase anxiety-like behavior. We use this in combination with a standardized procedure to characterize wound healing in mice, which relied on visual measurements of wound closure as well as cell type-specific examination of physiological indications of healing. We then compared social and anxiety-like behaviors with the efficiency of wound healing in adult mice with (n=12) or without a history of early life trauma (n=11). Results indicate that exposure to early life trauma is associated with wound closure and tissue regeneration occurring more slowly relative to non-stressed mice, suggesting that early life trauma incites lifelong deficiencies in immune function. This coincides with the behavioral impairments we observe following early life trauma, suggesting that a common underlying mechanism may mediate both psychological and physiological impairments induced by exposure to early trauma.

Disclosures: M. Nguyen: None. **L. Halladay:** None.

Poster

PSTR064. Early Neural Development

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Topic: A.08. Development of Neural Systems

Support: CIHR
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Canadian Foundation for Innovation
Brain Canada

Title: Microbe-immune mechanisms influencing postnatal brain development

Authors: *M. GREEN[1], G. CASPANI[4], S. R. CLEARY[2], B. KWIECIEN-DELANEY[2], J. A. FOSTER[3];
[1]Psychiatry and Behavioural Neurosciences, [3]Psychiatry, [2]McMaster Univ., Hamilton, ON, Canada; [4]Imperial Col. London, London, United Kingdom

Abstract: Recent decades of research have demonstrated the role of T-cells in orchestrating key neurodevelopmental processes. Several exciting discoveries have been made in this field, demonstrating the contribution of meningeal T-cells to CNS maturation and suggesting a role for the gut microbiome in modulating these T-cell dependent processes. However, our current understanding of how T-cells, gut microbes and the host CNS communicate and co-evolve during critical neurodevelopmental windows remains incomplete. This experiment performed deep phenotyping of wild type (WT) and T-cell deficient mice, the latter of which lack functional T-cells due to a double knockout of the β and δ chains of the T-cell receptor (*TCR β-/- δ-/-*).

Based on our recent work demonstrating the influence of microbe-T cell signalling on development of the brain metabolome, we hypothesized that such signals will also serve to regulate developmental patterns of gene transcription in the gut and the brain. RNA expression of targeted barrier integrity and neurotransmission genes were assessed in gut and brain tissue using Nanostring technology in male and female WT and *TCR β-/- δ-/-* mice, at postnatal day (P) 6 and P24. Functional T-cell subsets were measured over the first 4 postnatal weeks using flow cytometry, in parallel with composition and diversity of the gut microbiota via shotgun metagenomics. T-cell deficiency resulted in upregulation of tight junction (TJ) protein expression in the ileum compared to WT. Minimal genotype differences in TJ protein expression were observed in the colon, prefrontal cortex (PFC) and hypothalamus, suggesting normal development of the blood-brain barrier. *TCR β-/- δ-/-* mice displayed decreased expression of genes involved in the complement cascade (C4a, C1qa, C1qb) and microglial function (MafB, Dap12, Tmem119) in both brain areas under study, as well as a significant increase in BDNF transcription in the PFC. This is consistent with previous evidence demonstrating the role of T-cells in mediating microglial maturation and synaptic pruning, and suggests that T-cell deficiency delays the developmental trajectory of the gut-brain axis. The temporal regulation of genes related to microglia and dopaminergic signalling from pre- to post-weaning was paralleled by a significant increase in microbiota diversity, as well as proliferation of T regulatory and Th17 lamina propria and intraepithelial lymphocytes in the small intestine. Taken together, our results provide further insight into the developmental programming of the gut-brain axis through peripheral immune mediators, and their influence on hierarchical wiring of CNS circuitry.

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Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.19/C17

Topic: A.08. Development of Neural Systems

Support: 5R01MH1119118

Title: Investigating sex differences in biobehavioral endophenotypes under different models of inescapable stress

Authors: *L. BRYAN[1,2], D. FORTUNA[3], H. MCBRIDE[3], N. SUDHIR[2], K. R. ANDERSON[4,1], A. MANGANARO[1], D. DUMITRIU[1];
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Abstract: Sex differences compound individual variability in stress response. This stress predisposition or susceptibility in humans has consequences on a personal to global level, yet the mechanisms behind these two dimensions of variability are not fully understood. Divergent stress responses are therefore pertinent for study. To explore stress responses to different stressors and apply novel sex-equal approaches, our study exposes a cohort of mice to learned helplessness (LH) and then a novel sex-equal model of acute social defeat stress (ASDS). These two animal stress models provide binary stress phenotypic responses to study distinct neuronal activation maps during exposure to LH-shock and ASDS-defeat. An analysis of whole-brain activation was performed across both stressor and sex variables to explore differential activation. The behavioral results indicate a lack of sex-differences in LH, and sex-differences in social approach that ASDS stress attenuates. In a small analyzed subset, we also found no differences in the LH-induced activation of a few selected brain regions in relation to sex or stress. By further investigating stress-induced activation across these dimensions, our data will hopefully contribute to the stress field and offer a better understanding of the complex sex-differences in stress response as well as the behavioral stress model validity.

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Poster

PSTR064. Early Neural Development

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Program #/Poster #: PSTR064.20/Web Only

Topic: A.08. Development of Neural Systems

Support: FC-PD2022

Title: Rat hippocampal 5-HT1a receptor expression is altered by perinatal high calorie/low protein maternal diet

Authors: A. R. JIMENEZ-PEREZ, D. J. BUSTAMANTE-VALDEZ, M. A. FUENTES-CANO, ***P. DURAN**;
Facultad de Ciencias, UNAM, Mexico City, Mexico

Abstract: Serotonin acts as a growth factor during embryogenesis before assuming its role as a neurotransmitter. Its synthesis and release, as well as the activity of the serotonin receptor, are part of the cascade of events that lead to changes in the maturation of the central nervous system. Disruption in these processes can contribute to impaired development and alterations in the physiological and behavioral responses of the adult organism. Once established, the serotonergic system is one of the most relevant neurotransmitter systems in the brain, mainly due to its implications in critical neurophysiological processes such as regulation of the sleep-wake cycle, attention, learning and memory, mood, etc. Reports on alterations in their functioning reveal that they can lead to pathologies such as depression and anxiety, among other emotional disorders.

Malnutrition is one of the main non-genetic factors affecting brain development, negatively altering the organism's ability to interact with its environment. In addition, it is known that a deficiency in the quantity or quality of nutrients in the diet during pregnancy and lactation induces changes in the nervous system of the offspring with permanent consequences. Studies in prenatally malnourished animals have reported various alterations in the brain serotonergic system, specifically in hippocampal formation. Therefore, it is important to know whether a high-calorie, low-protein environment produced by a "cafeteria diet" during the prenatal and postnatal stages affects the development of the hippocampal serotonergic system, particularly the 5HT1a receptor, and what might be the Implications for developmentally related cognitive and behavioral processes. The results show that, in males, the relationship between receptor expression and cell number was maintained, despite exposure to perinatal malnutrition. In the control group, cell count and optical density revealed a difference between males and females: the female hippocampal CA1 showed fewer cells but higher expression of serotonin receptors. In the male hippocampus of control, and malnourished groups, a proportion close to 1:1 was presented, meanwhile, the malnourished female hippocampus presented a greater number of cells (ratio 1:1.5), but lower expression of serotonin receptors. We conclude that perinatal malnutrition caused by a high-calorie/low-protein diet decreases the expression of the 5HT1a receptor in the dentate gyrus and hippocampal CA1 of male and female rats. Furthermore, 5HT1a receptor expression in the CA1 hippocampus also exhibits sexual dimorphism in adult rats.

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Poster

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Topic: A.08. Development of Neural Systems

Support: PROSNI CUSUR UDG
Neurobiology Institute, UNAM;

Title: Effect of low protein diet intake during pregnancy and lactation on neurodevelopment of CA1 hippocampal in postnatal stage difference between males and females

Authors: *M. M. N. M. NAVARRO MEZA[1], M. NAVARRO MEZA[1], J. TRINIDAD GALLARDO[1], M. RODRÍGUEZ OSEGUERA[1], P. BELLO MEDINA[2], M. DÍAZ MUÑOZ[3]; [1]Dept. de Promoción, Preservación y Desarrollo de la Salud. Univ. de Guadalajara. Ciudad, Ctr. Universitario Del Sur/ Univ. De Guad, Ciudad Guzman/Jalisco, Mexico; [2]Univ. del Tolima, Ibagué, Tolima, Colombia, Inst. de Educación a Distancia IDEAD, Univ. del Tolima, Ibagué, Tolima, Colombia, Tolima, Colombia, Mexico; [3]Inst. de Neurobiología, Univ. Nacional

Autónoma de México, Querétaro, Querétaro, México., Inst. de Neurobiología, Univ. Nacional Autónoma de México, Querétaro, Querétaro, México., Queretaro Qro, Mexico

Abstract: The low protein diet intake (LPD) during pregnancy and lactation are related to cognitive alterations in the postnatal stage. Few studies evaluate the effect of maternal diets on the neurodevelopment of the hippocampus in the progeny. We evaluated LPD intake during pregnancy and lactation on 4′,6-diamidino-2-phenylindole (DAPI) and glial fibrillary acidic protein (GFAP) area ratio in hippocampal CA1 pyramidal stratum at postnatal (PN) day 10 in males and females. Female rats (*Wistar*) of reproductive age were used, divided in two groups: control (18% protein diet) and experimental (6% protein diet), food and water intake were quantified until day 10 of lactation; the brain slices of pups (males and females, n=6) were obtained to detect GFAP and DAPI in the pyramidal stratum of the hippocampus by immunohistochemistry, the images obtained by confocal microscopy were assessed in *ImageJ software* using double-blind method, two-way *ANOVA* and *post hoc* Bonferroni tests were performed. Male from experimental group showed a 19% increase in DAPI area ratio versus male control (*p=0.0017*); a 11.3% increase in DAPI signal in experimental males versus experimental females (p=0.019); 225.3% increase in GFAP signal in experimental males versus experimental females(p=0.010); and 124.4% increase in GFAP signal in experimental males versus control males(p=0.03). We suggest that male pups at day 10PN reflect more astrogliosis in CA1 hippocampus pyramidal area *versus* females as a protection mechanism to ensure the correct development of this neuronal structure.**Acknowledgements** The Authors would like to thank the following persons and institutions for their assistance and support of this study: José Martín García Servín, MVZ, for the handling and care of the experimental model; the Animal Care Facility of the Neurobiology Institute, UNAM; Nydia Hernández in the Microscopy and PhD, Vazquez-Martínez O for expert technical support.

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Poster

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Topic: A.08. Development of Neural Systems

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Title: A coming of age story: neurodevelopment of hypothalamic cell types controlling social behavior and homeostasis

Authors: *H. KAPLAN[1], K. ZHANG[3], J. XIAO[1], C. SANTIAGO[2], B. REN[4], D. D. GINTY[5], C. G. DULAC[6];

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Abstract: A coming-of-age story: neurodevelopment of hypothalamic cell types controlling social behavior and homeostasis

Mammalian social behaviors and homeostatic functions change dramatically during postnatal development: infants rely on mothers for food and warmth, juveniles eat and thermoregulate independently but are socially immature, and adults mate and parent. Molecular and systems neuroscience approaches have linked genetically identified cell populations in the preoptic area (POA) of the hypothalamus to the expression of distinct social behaviors and homeostatic regulations in adult mice, yet the organization, maturation and potential function of these circuits in younger animals remains unexplored.

To define the developmental trajectories of POA cell types, we generated paired transcriptomic and chromatin accessibility profiles of ~300,000 cells across 8 ages, from late embryo to adult. We identified ~150 neuronal types in this dataset, many of which could be mapped to previously identified cell types with well-studied and diverse functions such as parenting, thirst, and thermoregulation. The vast majority of these cell types were distinguishable in the late embryo, suggesting a potential parcellation of functional roles even before birth. Our analysis of the postnatal maturation of these cell types revealed key stages in POA neurodevelopment, including (1) arealization; (2) widespread and cell-type-specific changes in genes affecting neuronal signaling and physiology; and (3) perinatal and peripubertal cell-type-specific sexual differentiation.

We further found that individual cell types mature along diverse timelines: some gradually become adult-like postnatally, while others mature in a protracted, step-wise fashion, with changes concentrated around specific postnatal periods. To understand how these cell-type-specific trajectories are regulated, we examined chromatin accessibility changes over development and identified candidate enhancers, gene regulatory networks, and transcription factors. Finally, to determine how POA maturation is affected by sensory experience, we performed single-cell multiome experiments of POA in mutant strains impaired in olfaction, pheromone sensation, gentle touch, and thermosensation.

Altogether, our work delineates diverse, sex-specific, and experience-dependent maturational trajectories of key cell types involved in social behavior and homeostatic control, laying the foundation for future studies examining these functions in young mammals.

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Poster

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Topic: A.08. Development of Neural Systems

Support: R15 HD110963-01

Title: Transient disruption of vasopressin 1a signaling on embryonic day 16.5 has subtle effects on social interactions in adult mice

Authors: *K. REESE[1], H. K. CALDWELL[2];
[1]Biol. Sci., [2]Kent State Univ., Kent State Univ., Kent, OH

Abstract: There is growing evidence that vasopressin (Avp), and the closely related nonapeptide oxytocin (Oxt), have roles in neural development. Previous work from our lab found that transient disruption of Oxt receptor (Oxtr) signaling on embryonic day (E) 16.5 results in sex-specific behavioral effects in adult mice. Given that Avp and Oxt are closely related, that crosstalk often occurs between their receptors, and that the Avp 1a receptor (Avpr1a) is present and functional during embryonic development, it is reasonable to speculate that disrupting Avpr1a signaling during embryonic development will affect adult behavior. Thus, we hypothesized that transient disruption of Avpr1a signaling at E16.5 would impact adult behavior. To test this hypothesis, 2µL of either an Avpr1a antagonist (Avpr1aA) or vehicle was injected into the lateral ventricle of each embryo and behavioral testing performed when the offspring were at least 2 months old. Transient Avpr1a disruption had no effect on anxiety-like or depressive-like behavior, as measured in open field, elevated plus, and forced swim tests. There was also no effect of Avpr1a disruption on social discrimination in males or females. However, Avpr1aA-treated males showed decreases in affiliative behavior on Day 3 of resident-intruder testing. Additionally, Avpr1aA treated animals had impairments in social novelty preference during a 3-chamber test. These data suggest that disruption of Avpr1a signaling at E16.5 has subtle, but measurable, impacts on the neural development of brain circuitry important to the regulation of social behavior. Given these promising results, future studies will continue to investigate the contribution of embryonic Avpr1a signaling to brain development and behavioral endpoints.

Disclosures: K. Reese: None. **H.K. Caldwell:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.24/C20

Topic: A.08. Development of Neural Systems

Support: U54 MD007601
P20 GM139753

Title: Selenium deficiency impairs maturation of perineuronal nets and GABAergic inhibitory tone

Authors: A. SASUCLARK[1], ***M. PITTS**[2];
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Abstract: Selenoproteins are fundamental players in redox signaling that are essential for proper brain development and function. They are indispensable for the vitality of GABAergic parvalbumin-expressing interneurons (PVIs), a cell type characterized by fast-spiking activity and heightened rates of metabolism. During development, PVIs are preferentially encapsulated by specialized extracellular matrix structures, termed perineuronal nets (PNNs), which serve to stabilize synaptic structure and act as protective barriers against redox insults. These structures act as insulators that reduce membrane capacitance, thereby permitting PVIs to fire at heightened frequencies necessary to synchronize activity of neuronal assemblies. Consequently, alterations in PVIs and PNNs are well chronicled in neuropsychiatric disease, and evidence from animal models indicates that redox imbalance during adolescence impedes their maturation. Herein, we examined the influence of selenium on PNN development in primary cortical cultures. Parallel studies to monitor *in vitro* electrophysiological activity were conducted using microelectrode arrays (MEA). Cultures grown in selenium-deficient media exhibited reduced antioxidant activity and impaired PNN formation at 28 days *in vitro*, which coincided with reduced inhibitory perisomatic input onto PVIs. Selenium also affected the electrophysiological profile of developing cultures, as selenium deficient cultures exhibited impairments in long-term potentiation in conjunction with reduced spike counts for both network bursts and in response to stimulation. Finally, similar PNN deficits were observed in the cortex of mice raised on a selenium-deficient diet, providing corroborative evidence for the importance of selenium in PNN development. In sum, these findings show the vital role of selenium for the development of GABAergic inhibitory circuits.

Disclosures: A. Sasuclark: None. **M. Pitts:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.25/C21

Topic: A.01. Neurogenesis and Gliogenesis

Title: Assessment of the high confidence ASD gene WAC in a novel mouse model

Authors: *D. PACHECO CRUZ[1], A. M. STAFFORD[2], D. VOGT[1];
[2]Pediatrics and Human Develop., [1]Michigan State Univ., Grand Rapids, MI

Abstract: DeSanto-Shinawi Syndrome (DESSH) is a rare neurodevelopmental disorder caused by mutations in the WW-domain containing adaptor with coiled coil gene (*Wac*). In humans, DESSH presents with cognitive and behavioral symptoms that include seizures, attention deficit hyperactivity disorder (ADHD), and autism. Clinical management of the condition is focused on alleviating the symptoms, since the mechanisms that underlie DESSH are unknown. Animal

models of DESSH were lacking and mammalian models were urgently needed to address potential mechanisms. Our lab generated and characterized the first clinically relevant model of DESSH in mice, but further characterization of the model was still needed to understand the role of specific brain cells that underlie DESSH symptoms. One of the main comorbidities presented in DESSH is epilepsy and other seizure disorders, and we wanted to assess seizure susceptibility by deleting *Wac* from the cortical excitatory neurons to further explore the mechanistic role of this neuronal population in DESSH symptomatology. To characterize the behavioral and cognitive phenotypes our model is presenting, I performed several behavioral, molecular and cellular assays, as well as a seizure susceptibility assessment to determine cell types involved and temporal emergence of each phenotype. Our results will provide a better understanding of the roles of select neuronal populations in this mouse model of DESSH and help provide novel insights into how the *Wac* gene regulates normal brain development.

Disclosures: D. Pacheco Cruz: None. **A.M. Stafford:** None. **D. Vogt:** None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.26

Topic: A.08. Development of Neural Systems

Support: SFARI Bridge to Independence Award

Title: Striatal regulation of cortical activity and E/I balance during postnatal development

Authors: *R. PEIXOTO;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The postnatal maturation of cortical circuits is highly regulated by experience and activity-dependent mechanisms. 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, if and 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 circuit loops. To directly test whether manipulations of striatal circuits affect cortical activity during postnatal development, we ablated D1 and D2 MSNs unilaterally in dorsomedial striatum (DMS) of D1-Cre or A2A-Cre mice by cell-autonomous apoptosis using Cre-dependent Caspase3. In the same pups, AAV-syn-jGCaMP8s was injected in L2/3 of both dorsal anterior cingulate cortices (dACC) to characterize neuronal activity at P13, P16 and >P60. GCaMP8s activity was imaged simultaneously in both hemispheres using a large field-of-view 2-photon microscope. Our results show that ablation of D1 MSNs decreases the frequency of

spontaneous neuronal cortical activity in ipsilateral dACC compared to the contralateral hemisphere as early as P13. By contrast, ablation of D2 MSNs, increases the frequency of spontaneous cortical activity later at P16 that persists up to adulthood (P60). In addition, we further characterized how unilateral ablations of striatal D1- or D2-SPN alters the development of upstream cortical circuits by performing whole-cell recordings of excitatory and inhibitory miniature postsynaptic currents (mPSCs) in L2/3 pyramidal neurons (PNs). Ablation of both D1- and D2-SPNs in DMS had minimal effect on the frequency and amplitude of mEPSC in dACC PNs. However, ablation of D2-SPNs significantly decreased inhibitory connectivity onto PNs and resulted in a 1.5-fold decrease in mIPSC frequency. Notably, D1-SPN ablation induced the opposite effect and increased mIPSC frequency by 1.4-fold. Together, these results indicate the striatum modulates the activity of CSTC circuits from very early postnatal stages and provide the first demonstration that striatal circuit activity can bidirectionally regulate the establishment of inhibitory connectivity in upstream cortical circuits, effectively altering E/I balance.

Disclosures: R. Peixoto: None.

Poster

PSTR064. Early Neural Development

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.27/C22

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant S10OD019960
National Institute of Drug Abuse grant 1U01DA058278

Title: Single-nucleus multiome and spatial transcriptomics reveal abnormal neural development in rat brain after prenatal e-cigarette exposure

Authors: *C. WANG[1], Z. CHEN[2], W. CHEN[2], C. NEPAL[2], Y. LI[3], F. ZENG[2], L. SONG[2], W.-X. SHI[4], D. XIAO[3];
[2]Ctr. for Genomics, Sch. of Med., [3]Ctr. for Perinatal Biology, Sch. of Med., [4]Sch. of Pharm., [1]Loma Linda Univ., Loma Linda, CA

Abstract: Our study showed that prenatal e-cig exposure promoted excitatory neural differentiation and disrupted excitatory/inhibitory neuron balance in the postnatal day 7 (P7) rat brain. To examine the long-term effects of prenatal e-cig exposure and to examine the cis-regulatory potential of the key genes, we profiled gene expression and chromatin accessibility (snRNA-seq and snATAC-seq) from the same nucleus on 3-month-old rat brain prenatally exposed to e-cig. Overall, we obtained both single-nucleus transcriptomes and chromatin accessibility from over 31,000 nuclei. More than 2,000 genes and 20,000 high quality fragment peaks per single nucleus were detected. We identified chromatin open regions in more than 10,000 genes out of the 19,000 genes detected in snRNA-seq, with over 20% of the chromatin open regions overlapping with transcription start site. Several transcription factors (TF) were

enriched through DNA motif binding search from the differential chromatin accessibility regions induced by prenatal e-cig exposure, such as Ddit3 and Nr4a2. The functions of the enriched TFs were tightly associated with neural differentiation and function, such as cell cycle arrest, apoptosis, and regulating of dopaminergic neuron function. Gene Ontology and KEGG analyses based on snRNA-seq data showed that the differential expressed genes were enriched in the biological process of regulation of membrane potential, learning or memory, cognition, dopaminergic and glutamatergic synapse. These results suggest that the detrimental effects of prenatal e-cig exposure exist in the 3-month offspring brain. To further identify specific brain regions that are most susceptible to prenatal e-cig exposure, we generated spatial transcriptomic datasets from P7 rat brain sections using Visium Spatial (10x Genomics) and Stereo-seq technologies (STOmics). This information can be used to gain insight into the molecular basis of spatial effects following prenatal e-cig exposure.

Disclosures: **C. Wang:** None. **Z. Chen:** None. **W. Chen:** None. **C. Nepal:** None. **Y. Li:** None. **F. Zeng:** None. **L. Song:** None. **W. Shi:** None. **D. Xiao:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.01/C23

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: NIH grant R01DC011099
NINDS grant R21NS085772
NIMH grant RF1MH120016

Title: Complexity of connexin composition at post-synaptic sites of electrical synapses on the Mauthner cell

Authors: H. HOFF[1], *S. IJAZ[1], F. ECHEVERRY[1], J. O'BRIEN[2], A. PEREDA[1];
[1]Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY;
[2]Ophthalmology & Visual Sci., Univ. of Houston, Houston, TX

Abstract: Auditory ‘mixed’ synaptic contacts on the Mauthner neuron support both electrical and chemical transmission, and are known as “Club endings” (CEs). While the functional and structural diversity of chemical synapses is well established, the organization of gap junction (GJ)-mediated electrical synapses remains less understood. Studies conducted on goldfish and zebrafish have revealed the presence of two mammalian homologs of Cx36 (gjd2), Cx35 (gjd2) and Cx34 (gjd1), forming heterotypic channels, with Cx35 restricted to the presynaptic side and Cx34 to the postsynaptic side. In zebrafish (ZF), there are two orthologs of Cx35 (Cx35.1 and Cx35.5) and two orthologs of Cx34 (Cx34.1 and Cx34.7). Recent functional, electrophysiological, and immunohistochemical analyses of mutant and chimeric fish have determined that Cx35.5 and Cx34.1 asymmetrically localize to the pre- and postsynaptic sites,

respectively, of CE synapses onto Mauthner neurons. Additionally, in these mutants, the loss of Cx34.1 and Cx35.5 led to the abolishment of electrical transmission, indicating that these Cxs are required for electrical transmission. To gain further insight into the composition of CE GJs, we generated transgenic zebrafish in which these orthologs were fluorescently tagged. We confirmed a widespread distribution of transgene expression in Cx34.1 transgenic animals using immunohistochemistry. Unexpectedly, we found additional expression of Cx34.7. However, unlike Cx34.1, the expression of Cx34.7 was lower and distributed non-uniformly within a single CE, and its presence varied amongst these terminals. Expansion Microscopy analysis revealed that while all GJs contained Cx34.1, Cx34.7 co-localized with Cx34.1 in only a fraction of them. In contrast, analysis of Cx35.1 transgenics confirmed that Cx35.5 is the predominant connexin at presynaptic hemiplaques. Moreover, the evidence suggests the existence of a hierarchical organization between Cx34.1 and Cx34.7. That is, because Cx34.7 does not compensate for the loss of electrical transmission in Cx34.1 mutants, it suggests that Cx34.1 operates as the obligatory postsynaptic connexin, while Cx34.7 is non-obligatory and potentially recruited during specific functional contexts. In summary, our data indicate a complex asymmetry in the molecular organization of electrical synapses at CEs, which includes the presence of two connexins with distinct functional roles at postsynaptic sites.

Disclosures: H. Hoff: None. **S. Ijaz:** None. **F. Echeverry:** None. **J. O'Brien:** None. **A. Pereda:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.02/C24

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: NSF IOS 1557474
NIH R01 NS128713
Whitehall Foundation

Title: Functionally distinct thalamocortical circuits are linked by heterocellular electrical synapses in the thalamic reticular nucleus

Authors: *M. VAUGHN[1], Z. LASWICK[3], H. WANG[4], J. S. HAAS[2];
[2]Lehigh Univ., [1]Lehigh Univ., Bethlehem, PA; [3]Northwestern Univ., Evanston, IL; [4]Dept Physiol., SIU Carbondale, Carbondale, IL

Abstract: The thalamic reticular nucleus (TRN) inhibits thalamocortical relay and is a key regulator of sensory attention as well as sleep and wake states. Recent developments have identified two distinct genetic subtypes of TRN neurons, calbindin-expressing (CB) and somatostatin-expressing (SOM) neurons. These subtypes differ in localization within TRN, electrophysiological properties, and importantly, synaptic interactions with thalamocortical relay

channels. CB neurons send inhibition to and receive excitation from first-order thalamic relay nuclei, while SOM neurons send inhibition to and receive excitation from higher-order thalamic areas. These differences create distinct channels of information flow. The TRN has a dense concentration of gap junctions composed of connexin36. It is unknown whether TRN neurons form electrical synapses between SOM and CB neurons that consequently bridge first-order and higher-order thalamic channels. Here, we investigated electrical connectivity with two different methods: dual patch clamping of pairs and a novel, high-throughput optogenetic approach to map coupled networks. First, we recorded from patched pairs in CB-Cre and SOM-Cre mice crossed with a GFP reporter. We found coupling within and between both labeled and unlabeled neurons in each mouse type. Next, we expressed soma-targeted ChroME in Cre-expressing neurons through viral injection and recorded from either single labeled or unlabeled neurons. Then, we systematically photostimulated individual neighboring opsin-expressing neurons using a digital mirror device while imposing rheobase stimuli to the recorded neuron. Electrical synapses to the recorded neuron were identified by significant decreases in evoked spike latency when neighboring opsin-expressing neurons were individually photostimulated. Using this method, we confirmed that SOM-expressing neurons form electrical synapses with both expressing and non-expressing counterparts. Therefore, we conclude that electrical synapses link both within and across subtypes of neurons in TRN, forming either homocellular or heterocellular synapses and functionally linking first-order and higher-order thalamocortical relay channels. Our optogenetic approach can be used as a high-throughput method to identify and measure electrically coupled networks throughout the live brain.

Disclosures: **M. Vaughn:** None. **Z. Laswick:** None. **H. Wang:** None. **J.S. Haas:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.03/C25

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: DIRP, NIMH, USA, ZIAMH002797

Title: Exploring the roles of gap-junctional coupling in the brain

Authors: *S. PAJEVIC;
Natl. Inst. of Mental Hlth., NIH, Bethesda, MD

Abstract: When studying brain networks, the primary focus is mostly on neurons and their synaptic connectivity. In this study, we examine the functional role of gap-junctional coupling (GJC) and its lattice-like networks, which are formed not only between neurons but also between glia. GJC is a pronounced feature in many brain areas and nuclei (cortical and subcortical), whose formation can be traced early in brain development, between neurogliaform cells. Gap junctional coupling of astrocytes is their dominant feature in many brain regions, having five

types of connexins that they express, compared to three in neurons and four in oligodendrocytes. The role of such networks has been frequently associated with increased uptake and buffering capacities, but here we explore alternate functional roles. It has already been shown that GJC organization is related to the function, for example anisotropic and tonotopic organization of astrocytic gap-junctions in lateral superior olive; however, here we focus on the thalamic reticular nucleus (TRN) and its reticular/lattice-like cellular structure. The TRN holds a unique position in the brain, as it is traversed by thalamocortical connectivity passing through its mesh of glial cells and inhibitory neurons. It is implicated in attention, action, and plays a critical role in regulating the transmission of sensory information to the cortex. In spite of its importance characterization of TRN is difficult and many of its important features are not yet elucidated, including the precise relationships between GJC lattice-like network and the activity in the thalamocortical axons. Lacking such information, we use an idealized model to derive the relation between the spatiotemporal pattern of neuronal activations and the collective modes in such lattices, suggesting its role as a transducing element between neural activity and mental states. In it we utilize biophysics of the extracellular spaces in the GJ plaques whose electronic structure suggests novel excitation and transport properties. In general, GJCs have appeared early in the evolution of multicellularity, so to establish how early in evolution such dynamical properties might have appeared we propose long-term experiments that can be performed on simpler multicellular organisms, grown in diluted D2O, and we expect the mutation rates in the innexin/connexin channels to be elevated compared to the overall mutation rate. With the increased characterization of neural and gap-junctional connectivity, we expect to enhance our model predictions beyond what is currently provided with our idealized model, whose main role is only to elucidate its basic principles.

Disclosures: S. Pajevic: None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.04/C26

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: Research Manitoba Master's Studentship Award 5168
NSERC Grant RGPIN-05477-2017
CIHR Grant PJT-173550

Title: Pannexin 2 is a constitutively active chloride channel with similar yet distinct properties from Pannexin 1

Authors: *C. L. HUMPHREYS[1,2], N. E. LAVINE[1,2], M. F. JACKSON[1,2];
[1]Pharmacol. and Therapeut., Univ. of Manitoba, Winnipeg, MB, Canada; [2]PrarieNeuro Res. Ctr., Kleysen Inst. for Advanced Med., Winnipeg, MB, Canada

Abstract: Pannexins are ion channels which can release molecules up to 1kDa. Of the three pannexin isoforms, Pannexin 1 (Panx1) is studied most, implicated in several pathological states. While Panx1 is highly expressed during brain development, Panx2 expression dominates in the adult. Few reports have characterized the properties of channel Panx2, which may stem from a dogma that Panx2 primarily functions as an intracellular protein, which is difficult to reconcile given its suggested role in mediating ionic dyshomeostasis in ischemia. We now report prevalent, though not exclusive, Panx2 expression at the plasma membrane (PM) thus positioning us to explore the role and properties of Panx2 as a PM channel. Immunocytochemistry was used to evaluate surface localization of Panx1 compared to Panx2 when expressed in HEK293T. To assess relative subcellular distribution of each channel, cells were treated with wheat germ agglutinin (WGA, a PM marker) and an anti-calnexin antibody (an endoplasmic reticulum marker). We find colocalization of Panx2 with both markers, while Panx1 colocalizes tightly with WGA. This supports prevalent expression of Panx2 at the PM. To explore the role and properties of Panx2 as a membrane channel, we performed whole-cell recordings in HEK293T cells expressing Panx2 or Panx1. Current-voltage (IV) properties were examined by applying voltage ramps (±100mv, 500ms). Ramp-evoked currents for Panx2 and Panx1 were outwardly rectifying with negative reversal potential, suggesting that Panx2 may be primarily chloride permeable, as reported for Panx1. When extracellular chloride was replaced using sodium glutamate, current at +100mV was abolished, whereas no change was seen when extracellular sodium was replaced with NMDG-Cl. This affirms chloride as the major component of constitutive currents in Panx1/2. Due to lack of knowledge regarding Panx2 activation, we sought to examine whether Panx2 shares a mechanism with Panx1. Cell swelling due to hypotonic stimulus activates Panx1, but we show Panx2 is unaffected. Thus, Panx2 is constitutively active but does not respond to mechanical stimulation. Lastly, we have begun to assess the extent which Panx1/2 share sensitivity to pharmacological agents. We confirm previous reports that Panx2 is insensitive to carbenoxolone, an established Panx1 blocker. In contrast to a previous study, we show that DCPIB inhibits both Panx1/2-mediated currents. Unitedly, by studying the localization, PM current, ion flux and pharmacology of Panx1 and Panx2, we show Panx2 distinguishes itself from Panx1. Panx2 conducts current at the PM, indicating it is functional in this state, and should be recognized more widely as such.

Disclosures: C.L. Humphreys: None. **N.E. Lavine:** None. **M.F. Jackson:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.05/C27

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

Support: HHMI

Title: A periodic organization of endoplasmic reticulum-plasma membrane contact sites organizes Ca^{2+}release units allowing long distance propagation of Ca^{2+}signals

Authors: *L. BENEDETTI[1], R. FAN[2], A. WEIGEL[1], A. S. MOORE[1], M. A. KITTISOPIKUL[1], G. PARK[1], A. PETRUNCIO[1], P. M. HUBBARD[1], S. PANG[3], S. XU[3], H. HESS[1], V. RANGARAJU[2], S. SAALFELD[1], P. V. DE CAMILLI[4], T. A. RYAN[5], J. LIPPINCOTT-SCHWARTZ[1];
[1]4D Cell. Physiol., HHMI Janelia Res. Campus, Ashburn, VA; [2]Max Planck Florida Inst. for Neurosci., Max Planck Florida Inst. for Neurosci., Jupiter, FL; [3]Cell. and Mol. Physiol., Yale Univ. Sch. of Med., Ashburn, VA; [4]HHMI/Yale Univ., HHMI/Yale Univ., New Haven, CT; [5]Weill Med. College, Cornell Univ., Joan and Sanford I Weill Med. Col. of Cornell Univ., New York, NY

Abstract: The unidirectional relay of information over long distances in neurons represents a unique challenge for integration and propagation of intracellular signaling. An ideal candidate to facilitate this function is the endoplasmic reticulum (ER), which establishes extensive contacts with the plasma membrane (PM) as it extends from the cell body to dendritic elements and the peripheral axon. Here, we demonstrate that ER-PM contact sites formed by clusters of ER-PM tethering proteins periodically tile the plasma membrane of dendrites at 1 μm intervals. The fine architecture and distribution of these ER-PM contact sites seen in volumetric FIB-SEM data sets of neurons was conserved in both mouse hippocampus and *Drosophila* hemibrain. Notably, these contact sites were populated by key molecular components of Ca^{2+} release units (CRUs): Ryanodine receptors, Junctophilins and Voltage-gated calcium channels, suggesting a potential role of the ER-PM contact sites in Ca^{2+} signaling integration. Consistent with this possibility, two-photon glutamate uncaging at single spines led to Ca^{2+} release from ER with a spatial periodicity approximating 1 μm and spanning a ~ 30 μm distance from the stimulated spine. The propagating Ca^{2+} release signal depended on RyR function, whose receptors were at the periodically-distributed ER-PM contact sites. Together, the results identify a novel organization of the ER in neuronal processes comprised of periodic ER-PM contact sites that harbor molecular machinery capable of fine tuning Ca^{2+} homeostasis and propagating local Ca^{2+} signals over long distances to support intracellular signaling integration.

Disclosures: L. Benedetti: None. **R. Fan:** None. **A. Weigel:** None. **A.S. Moore:** None. **M.A. Kittisopikul:** None. **G. Park:** None. **A. Petruncio:** None. **P.M. Hubbard:** None. **S. Pang:** None. **S. Xu:** None. **H. Hess:** None. **V. Rangaraju:** None. **S. Saalfeld:** None. **P.V. De Camilli:** None. **T.A. Ryan:** None. **J. Lippincott-Schwartz:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.06/C28

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01MH124351
R01MH132226
U18DA052504

Title: Proteomic-based interactome of Nav1.6 reveals sex-specific biosignatures of resilience and vulnerability

Authors: *N. GOODE, S. MOHANTY, L. KOFF, J. DI RE, T. J. BAUMGARTNER, P. ARMAN, J. SINGH, G. GOLOVKO, L. K. PALMER, W. RUSSELL, F. LAEZZA;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Resilience and vulnerability to neuropsychiatric disorders are linked to molecular changes underlying excitability that are still poorly understood. In previous studies, we identified the voltage-gated Na^+ channel Nav1.6 as a mediator of neuroplasticity induced by environmentally enriched (EC) or isolated (IC) conditions which are used as models for resilience and vulnerability. Protein-protein interactions play a key role in regulating Nav1.6 channel function and whether the relative composition of the Nav1.6 interactome in EC/IC models is different is not known. This study aimed at characterizing the interactome of Nav1.6 in EC/IC models to search for proteomic-based biosignatures of maladaptive plasticity underlying resilience and vulnerability to neuropsychiatric disorders. The hypothesis tested in this study was that the Nav1.6 protein-protein interaction network is differentially regulated by EC/IC in the striatum and hippocampal regions. To determine the impact of the EC/IC behavioral paradigm on the composition of the Nav1.6 channel macromolecular complex, we housed rats in environmentally enriched (EC) and isolated conditions (IC) for 30 days (n= 24; 6 males and 6 females per condition). We used affinity purification from crude membrane extracts of the striatum and hippocampus of these rats followed by nanoLC/MS/MS to resolve the identity of Nav1.6 protein interactors. The Nav1.6 immunoprecipitated fractions of EC and IC rats revealed 165 and 63 protein interactors of Nav1.6 differentially expressed in the striatum and hippocampus, respectively. PANTHER protein class analysis revealed that most of the differentially expressed proteins in the striatum and hippocampus are involved with RNA metabolism (19%) and translation (25%), respectively. Classification by biological process revealed 31% of proteins in the striatum and 34% of proteins in the hippocampus are involved in cellular processes. Also, 32% and 31% of proteins in the striatum and hippocampus respectively are binding while 23% (striatum) and 25% (hippocampus) have catalytic activity. Our results support the hypothesis that the Nav1.6 protein-protein interaction network is differentially regulated by the EC/IC behavioral paradigm and offers valuable information for identifying new molecular targets suitable for the development of novel neurotherapeutics.

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Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.07/C29

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: K99NS125102

Title: Targeting the mechanosensitive K^+ channel TRAAK with ultrasound to modulate neuronal electrical excitability.

Authors: *B. SORUM[1], T. DOCTER[2], S. BROHAWN[2], R. RIETMEIJER[3], V. PANICO[2]; [1]Helen Wills Neurosci. Inst., [2]Mol. & Cell Biol., [3]Biophysics, Univ. of California, Berkeley, Berkeley, CA

Abstract: TRAAK is a mechanosensitive two-pore domain K^+ (K2P) channel found in nodes of Ranvier of myelinated axons of the white matter. It displays low leak activity at rest and is activated up to 100x by increasing membrane tension. Our recent structural and functional studies have led to biophysical models for channel gating and mechanosensitivity, where we demonstrated that basal and mechanically gated openings are clearly distinct states and are distinguished by their conductance, kinetics, and structure. This was visualized in single-channel recordings, which showed dual modes of activity and provided a basis for the development of novel treatments such as ultrasound (US) neuromodulation. US stimulation modulates the electrical activity of excitable cells, including in the brain's deep structures. However, the molecular basis underlying the effects of US on neural activity is still elusive and is currently under investigation. Using inside-out patch electrophysiology, we performed single-channel recordings of TRAAK in Xenopus oocytes to better understand the molecular basis of US-induced channel activation. Consistent with larger currents, single-channel activity was low under basal conditions and increased upon US stimulation (10 ms, 5 MHz, 0.34-1.2 W/cm^2). Single channels were confirmed to be TRAAK by their K+ selectivity, unitary conductance of ~73 pS at positive potentials (150 mM KCl bath, 15 mM KCl pipette), and characteristic "flickery" brief openings and a subconductance state. In mouse brain slices, US stimulation (10 ms, 5 MHz, 3.6 W/cm^2) activated large currents in TRAAK-ST-mRuby-expressing neurons, with a mean peak activation of ~400 pA at 0 mV. During spike trains, pulsed US stimulation resulted in a ~3 mV reduction in spike amplitude. We then used simultaneous patch-clamp recording and fluorescent imaging to quantify these results to determine TRAAK's tension response to US. TRAAK was activated by membrane tension, calculated with the Laplace equation (Tension = ΔPressure * radius of curvature / 2), over a broad range from low to near lytic tension. Data across patches were well fit to a Boltzmann with a midpoint tension of T_{50}=4.7 ± 0.2 mN/m and 10-90% range of 1.4-8.1 mN/m (mean ± SEM, n = 5 patches). This graded response profile distinguishes TRAAK from similarly low-threshold mechanosensitive channels Piezo1 and MscS, which activate in a step-like fashion over a narrow tension range. These results provide mechanistic insight into TRAAK tension gating, a framework for exploring the role of mechanosensitive K^+ channels at nodes of Ranvier, and a biophysical context for developing US as a mechanical stimulation technique for neuromodulation.

Disclosures: B. Sorum: None. **T. Docter:** None. **S. Brohawn:** None. **R. Rietmeijer:** None. **V. Panico:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.08/C30

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

Support: ANR-20-CE17-0013
ANR-20-CE14-0016

Title: Insulin regulates P2X4 receptor function and surface trafficking/mobility

Authors: *E. BOUE-GRABOT[1], S. CARRACEDO[1], E. COME[2], T. DELUC[3], E. EISELT[1], E. BERTIN[1], A. GEZER[1], M. RUSSEAU[2], A. ASE[3], P. SEGUELA[3], S. LEVI[2];
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Abstract: P2X receptors (P2X) are ATP-gated non-selective cation channels highly permeable to calcium widely expressed in many tissues where they participate in synaptic neuromodulation and neuroglial communication, inflammation, chronic pain or vascular tone. P2X4 are constitutively internalized by dynamin-dependent endocytosis and mainly retained intracellular in basal conditions. P2X4 have been shown to be upregulated at the surface of cells in various pathophysiological contexts indicating the importance of the regulation of P2X4 function and trafficking. Insulin was previously shown to modulate the trafficking and function of $GABA_A$ and AMPA receptors in CNS neurons. Here we show that insulin induces a rapid and long-lasting increase of the amplitude of ATP-evoked currents in *Xenopus* oocytes expressing mammalian P2X4 receptors. Insulin blocks also the rundown of P2X4 responses observed during repeated application of ATP. In contrast, no change in ATP responses from oocytes expressing P2X2 or P2X3 receptors is observed in the presence of insulin. Internalization-deficient P2X4 mutant responses are potentiated in a similar manner by insulin. Western blot analysis of surface biotinylated and total protein fractions from oocytes shows that insulin increases the number of surface wild-type and internalization-deficient P2X4 mutants. Furthermore, ATP-evoked P2X4 currents and surface number of native P2X4 are significantly increased by insulin in mouse microglia as well as in native peritoneal macrophages from wild-type or knockin P2X4mCherryIN mice. The insulin-mediated increase of surface and function of P2X4 is abolished in presence of tyrphostin or TeTN, two blockers of insulin receptors and exocytosis, respectively. In addition, we took advantage of our P2X4mCherryIN model that increases surface P2X4, to study by single particle tracking the mobility of P2X4mcherryIN in transfected rat hippocampal neurons. We revealed for the first time that P2X4 are highly mobile on the dendritic extrasynaptic membrane of excitatory pyramidal neurons. In addition, P2X4 are slowed down and confined at the periphery of homer1c-GFP labeled glutamatergic synapses while they rarely enter into the glutamatergic synapse. We further showed that application of insulin causes a rapid increase in P2X4 membrane confinement as reported by the reduction in diffusion coefficient and surface exploration, which suggest increased anchoring of the receptor to scaffolding molecules. Altogether, these results show that insulin modulate P2X4 receptor function and mobility in various cell types very likely via delivery of new P2X4 channels to the surface.

Disclosures: **E. Boue-Grabot:** None. **S. Carracedo:** None. **E. Come:** None. **T. Deluc:** None. **E. Eiselt:** None. **E. Bertin:** None. **A. Gezer:** None. **M. Russeau:** None. **A. Ase:** None. **P. Seguela:** None. **S. Levi:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.09/C31

Topic: A.07. Developmental Disorders

Support: DFG CRC 1451 (B01)

Title: Role of I(h) in the development of motor dysfunctions

Authors: *G. MATHIAS[1], A. MERSEBURG[2], J. ERLENBECK-DINKELMANN[3], J. BOEHM[4], P. VOGEL[3], S. MARGUET[6], J. ROEPER[5], D. ISBRANDT[7];
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Abstract: Motor development and learning are crucial to interact with our environment. The developing brain, however, is vulnerable to insults that can lead to various neurodevelopmental disorders (NDDs), as seen in several ion channelopathies. Motor dysfunction is one of the most frequent common comorbidities of these NDDs. To study the consequences of the loss of HCN channel-mediated I(h) in mouse forebrain, we generated a transgenic mouse model expressing a conditional dominant-negative HCN subunit (HCN-DN), driven by the CaMKIIalpha promoter and controlled by the Tet-off system. Lifelong expression of HCN-DN channels impaired somatomotor development and led to adult hyperactivity. However, persistent locomotor hyperactivity could be observed even when the expression of HCN-DN subunits was restricted to the first three postnatal weeks. Acute recordings from S1 and V1 cortex suggested reduced cortical excitability during the first postnatal week, when cortex-driven striatal synaptogenesis occurs. We therefore focused on the spiny projection neurons (SPNs) and interneurons of the dorsolateral striatum (DLS), which receives inputs from the sensorimotor cortex. Whole-cell patch clamp recordings from the indirect pathway SPNs (iSPNs) showed a significant decrease in EPSP current frequencies for lifelong HCN-DN mice, suggesting a decrease in excitatory drive from the cortex to the iSPNs. To study the effect of iSPN activation on the locomotor hyperactivity phenotype, we crossed the HCN-DN model with an excitatory chemogenetic mouse line, Adora-2a rM3Ds, allowing us to specifically manipulate (iSPNs) using Compound 21 (C21). We could ameliorate the hyperactivity phenotype by activating the iSPNs in lifelong HCN-DN mice using C21. To identify changes in local field potential and unit activity in the DLS of lifelong HCN-DN mice, we performed multichannel in vivo depth recordings in awake

head-fixed or freely moving animals, between the ages of 3-12 weeks. We aimed to classify the different neuronal populations using their extracellular spike properties and response to C21. Preliminary results show changes in firing properties of striatal and cortical cells, with some cells decoupling their activity from movement after C21 administration.

Disclosures: **G. Mathias:** None. **A. Merseburg:** None. **J. Erlenbeck-Dinkelmann:** None. **J. Boehm:** None. **P. Vogel:** None. **S. Marguet:** None. **J. Roeper:** None. **D. Isbrandt:** None.

Poster

PSTR065. Neuronal Excitability and Signal Propagation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.10/C32

Topic: B.09. Glial Mechanisms

Support: NIH R01NS118747

Title: Glutamatergic activity regulation of exosomal packaging of miRNA and secretion in cortical neurons

Authors: *M. BERTOLIO, Q. LI, F. E. MOWRY, Y. YANG;
Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Neuronal exosomes have been shown to be involved in neural development, synaptic plasticity, regeneration, and neurodegeneration in which miRNAs (miRs) are important signal mediators. However, whether and how neuronal activity regulates miR packaging into endosome derived ILVs and subsequent exosome secretion remains largely unclear. By selectively inducing GFP-tagged exosome marker human tetraspanin CD63 (hCD63-GFP) in neurons, here we examined how glutamatergic signaling impacts intracellular trafficking of hCD63-GFP and exosomal secretion. Confocal image analysis found that hCD63-GFP signals are mostly centered (&gt 95%) in neuronal soma around nucleus, either highly overlapped with the late endosome marker Rab7 (90%) or abundantly (30%) co-localized with early endosome marker EEA1, but very lowly co-localized with Golgi apparatus (~10%) or nucleus (&lt 5%). Glutamate treatment induces an overall reduction and scattered hCD63-GFP signals in neuronal soma but is increased in neurites. Glutamate treatment has minimal impact on the co-localization of hCD63-GFP with subcellular organelle markers except slightly decreased co-localization with Rab7. Interestingly, although CD63 is thought to target plasma membrane, we observed no GFP fluorescence on plasma membrane, likely due to its fast internalization. Secreted exosome quantity was also analyzed using ZetaView nanoparticle tracking analysis (NTA) and found that acute glutamate treatment induces 40% increase of secreted exosome quantity. Small RNA cargoes in exosomes are being sequenced and analyzed to determine the impact of glutamate treatment on miR profile in exosomes. To determine whether neuronal activity stimulates exosome secretion in vivo, we conducted DREADD-based chemogenetic stimulation by co-injecting mixture of AAV8-DIO-hM3Dq-mCherry and AAV9-hSyn-Cre virus in somatosensory cortex and AAV9-hSyn-Cre

virus injection on the contralateral side of somatosensory cortex (as control) of exosome reporter hCD63-GFP$^{f/f}$ mice. Histological analysis following the injection found that hCD63-GFP signal was significantly more widespread compared to the control side, and clear hCD63-GFP fluorescence can be detected on sections far distal from the injection site compared to the control side, further suggesting an increase in the secretion and spreading of DREADD-stimulated neuronal exosomes. In summary, these findings demonstrated the stimulatory effect of glutamatergic activity on subcellular hCD63-GFP redistribution and neuronal exosome secretion, providing new insights on how activity affect EV-mediated intercellular communication in the CNS.

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Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.11/C33

Topic: B.03. Ion Channels

Support: Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Channelpedia 2.0: an updated and enhanced integrative and interactive database for ion channels

Authors: *K. JOHNSTON, E. SCANTAMBURLO, A. JOURNE, E. LOGETTE, M. HERZOG, M. JOFFRAUD, S. VAN DORP, K. ARULKANDARAJAH, H. MARKRAM, R. RANJAN;
Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL), Campus Biotech, 1202 Geneva, Switzerland, Geneva, Switzerland

Abstract: Over the past 40 years, extensive research has been conducted on ion channel's molecular, structural, and biophysical properties. Despite the vast amount of literature on ion channels, no public resource was available on raw data defining their biophysical properties. Hence, Channelpedia (https://channelpedia.epfl.ch) was created to serve as a comprehensive scientific resource, consolidating information about ion channels. The updated version of Channelpedia 2.0 includes enhanced front-end and back-end structures, optimized user navigation, as well as, for the first time, raw electrophysiology data from all voltage-gated ion channels. Additionally, we have developed an AI-based assistant prototype on Channelpedia, which enables users to access ion channel information through a natural language query interface. Channelpedia is one of the few freely available web-based platforms that contains curated information on ion channels; however, it is the only resource that contains publicly accessible raw electrophysiology data, making it a unique and valuable resource for ion channel research.

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Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.12/C34

Topic: B.03. Ion Channels

Support: NASA NM Space Grant
NMSU Foundation

Title: Expression of transporter and cytosketal genes in GeneLab murine spaceflight datasets

Authors: H. GATICA-GUTIERREZ, *E. E. SERRANO;
Biol., New Mexico State Univ., Las Cruces, NM

Abstract: Human space exploration and the global surge in plans to live on other planets impart urgency to research that seeks to understand the role of altered gravity on biological systems. On the Earth's surface, organisms have evolved under a consistent gravitational field. In contrast, the magnitude of the gravitational field varies during spaceflight and differs from that of Earth on other planetary surfaces. Cognition is critical for astronaut decision-making and safety during space travel, and therefore it is crucial to understand brain responses to altered gravity. This pilot study aimed to assess gene expression in neural tissue from specimens that experienced spaceflight. Our analysis focused on cytoskeleton genes that are essential for neural cell morphology and ion channel/transporter genes necessary for neural signaling and physiological function. We queried the NASA GeneLab open-access data repository and were able to identify a few datasets that reported neural data and met our other criteria. The experiments exposed *Mus musculus* to microgravity conditions aboard the International Space Station and subsequently acquired gene expression data from brain or retina. RNA-seq and microarray datasets for spaceflight and ground control samples were analyzed for differential gene expression (DGE), then filtered through curated lists for ion channel/transporter and cytoskeleton genes. Genes showing high levels of differential expression were further processed using Enrichr's Gene-set libraries to identify potential biological processes and molecular functions. Our analysis did not detect DGE in most samples. However, one murine retina experiment resulted in differential expression of cytoskeletal genes that gene ontology analysis assigned to processes such as supramolecular fiber organization and actin binding. The dataset also yielded differential expression of ion channel/transporter genes involved with intracellular pH and the basolateral plasma membrane. We observed that GeneLab spaceflight datasets can be challenging to analyze because they often have low sample numbers and few replicates. It was encouraging to note that cytoskeleton and ion channel/transporter genes were expressed at comparable levels under microgravity and ground control environments. Greater attention to the influence of a prolonged

altered gravity environment on neural gene expression is necessary to understand the impact of spaceflight on the nervous system and to ensure the well-being of humans during long-duration space missions.

Disclosures: H. Gatica-Gutierrez: None. **E.E. Serrano:** None.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.13/C35

Topic: B.03. Ion Channels

Support: HRSA-T99HP39202

Title: Behavior sensitization in ASIC1a knock-out mice in response to cocaine administration

Authors: W. OBERT, W. STARK, R. JILAKARA, Q. JIANG, ***M. WACKER**, X. CHU; Univ. of Missouri, Kansas City, Kansas City, MO, MO

Abstract: Acid-sensing ion channels (ASICs) are highly expressed in the brain and involved in the learning/memory, fear conditioning and pain. They also contribute to neurological and psychological diseases such as stroke, traumatic brain injury, depression-like behavior, and drug addiction. Although, the involvement of ASICs in cocaine addiction has been reported by using ASIC1 knock-out (KO) mice (2-month-old), the role of ASIC1a in cocaine addiction is not fully understood. In the present studies, ASIC1a KO mice were generated by using CRISPR/Cas9 technology at our university animal core. We examined the role of ASIC1a in response to acute and chronic cocaine administration in adult (6-month-old) ASIC1a KO mice. We conducted behavioral activities by measuring total distance, horizontal activity, and stereotyping time of the individual ASIC1a KO mouse. Acute cocaine injection at a dosage of 20 mg/kg (i.p. injection) induced an increase in locomotor activities in ASIC1a KO mice. In a chronic cocaine administration model (20 mg/kg, once daily for 5 days, i.p. injection), daily cocaine injection also triggered increased locomotor activities. Further, a challenge injection of cocaine (10 mg/kg, after 2-week withdrawal) caused an evident behavioral sensitization in the cocaine-pretreated, but not saline-pretreated ASIC1a KO mice. As compared to wide-type mice, the behavior sensitization in ASIC1a KO mice is much less. Our results demonstrate the important role of ASIC1a in the modulation of behavioral sensitivity to cocaine. Thus, targeting ASIC1a might be a potential therapeutic strategy for treatment of cocaine addiction.

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Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.14/C36

Topic: B.03. Ion Channels

Support: TKP-2021-EGA-05 from Ministry of Culture and Innovation of Hungary
EU's Horizon 2020 grant No. 739593
OTKA K 134279
National Brain Research Program Hungary

Title: Hcn channels at the cell soma ensure the rapid electrical reactivity of fast-spiking interneurons in human neocortex

Authors: *V. SZEGEDI[1], E. BAKOS[1], S. FURDAN[1], B. KOVACS[2], D. VARGA[2], M. ERDELYI[2], P. BARZÓ[3], A. SZűCS[1], G. TAMAS[3], K. LAMSA[1];
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Abstract: Accumulating evidence indicates that there are substantial species differences in the properties of mammalian neurons, yet theories on circuit activity and information processing in the human brain are based heavily on results obtained from rodents and other experimental animals. This knowledge gap may be particularly important for understanding the neocortex, the brain area responsible for the most complex neuronal operations and showing the greatest evolutionary divergence. Here, we examined differences in the electrophysiological properties of human and mouse fast-spiking GABAergic basket cells, among the most abundant inhibitory interneurons in cortex. Analyses of membrane potential responses to current input, pharmacologically isolated somatic leak currents, isolated soma outside-out patch recordings, and immunohistochemical staining revealed that human neocortical basket cells abundantly express hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel isoforms HCN1 and HCN2 at the cell soma membrane, whereas these channels are sparse at the rodent basket cell soma membrane. Antagonist experiments showed that HCN channels in human neurons contribute to the resting membrane potential and cell excitability at the cell soma, accelerate somatic membrane potential kinetics, and shorten the lag between excitatory postsynaptic potentials and action potential generation. These effects are important because the soma of human fast-spiking neurons without HCN channels exhibit low persistent ion leak and slow membrane potential kinetics, compared with mouse fast-spiking neurons. HCN channels speed up human cell membrane potential kinetics and help attain an input-output rate close to that of rodent cells. Computational modeling demonstrated that HCN channel activity at the human fast-spiking cell soma membrane is sufficient to accelerate the input-output function as observed in cell recordings. Thus, human and mouse fast-spiking neurons exhibit functionally significant differences in ion channel composition at the cell soma membrane to set the speed and fidelity of their input-output function. These HCN channels ensure fast electrical reactivity of fast-spiking cells in human neocortex.

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Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR066.15/C37

Topic: B.03. Ion Channels

Support: NIH Grant R01AA027065
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NIH Grant R01DK103901

Title: Cholinergic enteric neurons detect luminal pressure through Piezo1 to regulate gut motility

Authors: *Z. XIE[1], J. FENG[1], T. J. HIBBERD[2], Y. ZHAO[1], K. ZANG[1], X. HU[1], X. YANG[1], F. GAO[1], N. J. SPENCER[2], H. HU[1];
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Flinders Univ., Adelaide, Australia

Abstract: The enteric nervous system (ENS), known as the "second brain" in the gut, plays a crucial role in regulating gastrointestinal (GI) motility. The ability to sense luminal pressure in the GI tract is essential for proper peristalsis, digestion, and waste elimination. However, the molecular basis of mechanosensitivity in the ENS is poorly understood. Here we show that cholinergic neurons in the myenteric plexus abundantly express mechanically sensitive Piezo1 but not Piezo2 channels as genetic ablation of Piezo1 but not Piezo2 from cholinergic myenteric neurons reduces mechanically-activated membrane currents and $[Ca^{2+}]_i$ responses. By using an intersectional genetics strategy, we demonstrate that optogenetic activation of $Piezo1^+$ cholinergic enteric neurons accelerates colon motility both *ex vivo* and *in vivo*. More importantly, Piezo1 deficiency in cholinergic neurons decreases both *ex vivo* CMMC induced by increased luminal pressures and *in vivo* GI transit, and AAV virus-mediated knockdown of Piezo1 reduces colon motility. Our findings demonstrate that mechanosensitive Piezo1 channels expressed by cholinergic enteric neurons are required for normal GI motility, thereby identifying potential therapeutic targets for the treatment of GI motility-related disorders.

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Poster

PSTR066. Other Ion Channels

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.16/C38

Topic: B.03. Ion Channels

Title: The effect of zinc on the short and long gamma subunit splice variants of human GABAAreceptors

Authors: *A. YEHIA, N. HUNT;
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Abstract: $GABA_A$ receptors, which are targeted by sleep aids, anti-anxiety medications, anesthetics, alcohol and neurosteroids, regulate rapid inhibition in the mammalian brain. These receptors are made up of α, β and ɣ subunits and the ɣ subunit has two splice variants: S and L. These variants differ by 8 amino acids when integrated into the pentameric receptors. They have different patterns of distribution during development and in the adult brain, with L being more dominant in later stages of life. Although recorded ionic currents from these subunits tend to show little characterizing differences, this is not the case when Zinc is present. A microfluidics-based automated patch clamp assay was used to investigate the differences in ionic current between these two splice variants under different conditions. Data will be presented from splice variants of human α1β2ɣ2, α2β2ɣ2 and a3β2ɣ2 $GABA_A$ receptors.

Disclosures: A. Yehia: None. **N. Hunt:** None.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.17/C39

Topic: B.03. Ion Channels

Support: R21 AG067029

Title: The selective effects of N-terminal amyloid beta (Aβ) fragments on the single-channel properties of α7 and α7β2 nicotinic acetylcholine receptors (nAChR)

Authors: *C. F. ROBERTS[1], R. J. LUKAS[2], R. A. NICHOLS[3], A. A. GEORGE[1];
[1]Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA; [2]Mol. Matters AZ, LLC, Phoenix, AZ; [3]Univ. of Hawaii, Univ. of Hawaii, Honolulu, HI

Abstract: Background: Neuronal excitotoxicity is a feature of Alzheimer's disease (AD) and has been reported in humans and in mouse models of AD pathology. Recently, we have demonstrated that pathologically-relevant concentrations of oligomeric $Aβ_{1-42}$ ($oAβ_{42}$) exhibit agonist-like action on both human α7- and α7β2-nAChR. Interestingly, $oAβ_{42}$ preferentially alters the single-channel kinetics of α7β2-nAChR by enhancing α7β2-nAChR open-dwell times. Moreover, basal forebrain cholinergic neurons (BFCNs) exhibit neuronal hyperexcitation when chronically exposed to $oAβ_{42}$. This effect was eliminated in the presence of α7*-nAChR

antagonists or in $\beta2^{-/-}$ mice. These findings demonstrate specific cellular and intrinsic-level mechanisms through which $oA\beta_{42}$/a7β2-nAChR interactions enhance BFCN excitability. While $A\beta_{42}$ represents the longest and most toxic version, several truncated isoforms of Aβ are present within the central nervous system and have been shown to modulate presynaptic Ca^{2+} handling in hippocampal CA1 neurons via α7* nAChR associations. Methods: We examined functional interactions between $oA\beta_{42}$, the N-Aβ fragment, and the N-Aβcore hexapeptide (found within the N-Aβ fragment) using single-channel recordings of concatenated, human α7- and α7β2-nAChR heterologously expressed in nAChR-null SH-EP1 cells. Results: We demonstrate that when applied exclusively, full-length $oA\beta_{42}$ preferentially enhances heteromeric α7β2-nAChR single-channel open probability (P_{open}), total burst duration, and open-dwell times within bursts (compared to ACh administration alone). Application of the N-Aβ fragment alone or in combination with ACh or $oA\beta_{42}$ resulted in selective enhancement of homomeric α7-nAChR open-dwell times within bursts, and total burst duration (compared to ACh or $oA\beta_{42}$ administration alone). Conversely, α7β2-nAChR single-channel open-dwell times were abrogated in the presence of the N-Aβ fragment compared to $oA\beta_{42}$ administration alone. Administration of the N-Aβcore hexapeptide normalized $oA\beta_{42}$-induced enhancement of α7β2-nAChR single-channel P_{open}, open-dwell times within bursts, and total burst duration compared to ACh or $oA\beta_{42}$ administration alone. Conclusions: Since Aβ is involved in regulating various learning and plasticity behaviors, these findings could have significant implications for a wide range of cholinergically-mediated functions, including cognitive enhancement in dementias such as AD. Inquiry into these biologically active Aβ fragments opens an important avenue for understanding the role of Aβ/nAChR interactions in contributing toward neuronal and network-level instability and memory loss in AD.

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Poster

PSTR066. Other Ion Channels

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Program #/Poster #: PSTR066.18/C40

Topic: B.03. Ion Channels

Support: NIH Grant R35 NS097343
NIH Grant R01 MH046742

Title: Gating of homeostatic regulation of intrinsic excitabilityproduces cryptic long-term storage of prior perturbations

Authors: *L. M. ALONSO[1], M. C. P. RUE[2], E. MARDER[3];
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Abstract: Neurons and neuronal circuits must maintain their function throughout the life of the organism despite changing environments. Previous theoretical and experimental work suggests that neurons monitor their activity using intracellular calcium concentrations to regulate their intrinsic excitability. Models with multiple sensors can distinguishamong different patterns of activity, but previous work using models with multiple sensors produced instabilities that lead the models' conductances to oscillate and then to grow without bound and diverge. We now introduce a nonlinear degradation term that explicitly prevents the maximal conductances to grow beyond a bound. We combine the sensors' signals into a master feedback signal that can be used to modulate the timescale of conductance evolution. Effectively, this means that the negative feedback can be gated on and off according to how far the neuron is from its target. The modified model recovers from multiple perturbations. Interestingly, depolarizing the models to the same membrane potential with current injection or with simulated high extracellular K+ produces different changes in conductances, arguing that caution must be used in interpreting manipulations that serve as a proxy for increased neuronal activity. Finally, these models accrue traces of prior perturbations that are not visible in their control activity after perturbation but that shape their responses to subsequent perturbations. These cryptic or hidden changes may provide insight into disorders such as posttraumatic stress disorder that only become visible in response to specific perturbations.

Disclosures: L.M. Alonso: None. **M.C.P. Rue:** None. **E. Marder:** None.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.19/C41

Topic: B.03. Ion Channels

Support: Milken Family Foundation
Program for the Promotion of Interdisciplinary Team Science (POINTS) of Yale University

Title: A Novel Mitochondrial Target as a Therapeutic Approach to Bipolar Disorder

Authors: *L. SHEN, J. KIM, I.-H. PARK, H. BLUMBERG, E. JONAS;
Yale Univ., New Haven, CT

Abstract: A Novel Mitochondrial Target as a Therapeutic Approach to Bipolar Disorder Lei Shen, Jonghun Kim, In-hyun Park, Hilary Blumberg, Elizabeth Jonas*
Stem cell-derived 3D human brain organoids have the potential to recapitulate features of the human brain with greater complexity than 2D models and are increasingly being applied to model diseases affecting the central nervous system. Neurons derived from patient (hiPS) cells have also been used to model highly heritable yet idiopathic psychiatric disorders. Studies of hippocampal dentate gyrus-like neurons derived from patients with bipolar disorder have

previously revealed mitochondrial abnormalities and neuronal hyperexcitability compared with healthy controls (HC). A previous report from our lab had shown that neurons from an autism model mouse and patient cells had a leak in the ATP synthase in the inner mitochondrial membrane caused by an imbalance of ATP synthase components. The membrane embedded portion of the ATP synthase (c-subunit ring) was found to be overexpressed compared to the assembled ATP synthase and this resulted in formation of a leaky channel. We therefore determined if ATP synthase stoichiometry was affected in bipolar disorder (BD) in patient derived neurons. We measured ATP synthase subunits' protein expression in monocyte-derived pluripotent stem cells (iPSCs) derived from one BD and one HC and in human medial ganglionic eminence-like organoids (hMGE) and cortical-like organoids (hCO) from the BD and HC. We found ATP synthase β-subunit was not significantly changed while c-subunit was significantly increased in both types of organoids at 45 days and 75 days compared to those of the HC. In the iPSCs, we also found enhanced c-subunit expression.We hypothesized that the normal aerobic glycolytic metabolism of developing neurons is persistent in BD neurons due to hyperactivity of ATP synthase c-subunit leak channel (ACLC), leading to a persistent glycolytic metabolic phenotype at later developmental stages with high lactate production and reversal of ATP synthase to the hydrolytic mode. To determine any hyperactivity of ACLC, we recorded mitoplast activity in the BD and HC human organoids. We found that BD cortical organoid mitoplasts have larger peak conductances than those of HCs. Lithium, which is a long-term treatment for episodes of mania and depression, blocks ACLC in both BD and HC cortical organoid mitoplasts and appears to work synergistically with the known ATP synthase pharmacological modulator, dexpramipexole (Dex).

Disclosures: **L. Shen:** None. **J. Kim:** None. **I. Park:** None. **H. Blumberg:** None. **E. Jonas:** None.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.20/C42

Topic: B.03. Ion Channels

Support: CIHR Project Grant
NSERC Discovery Grant
Canadian Pain Society
Mitacs
International Association for the Study of Pain
Eli Lilly

Title: Heterogeneity of synaptic NMDA receptor responses within individual lamina I pain processing neurons across sex in rats and humans

Authors: *A. DEDEK[1], E. TOPCU[3], C. DEDEK[4], J. S. MCDERMOTT[5], J. L. KRAJEWSKI[6], E. C. TSAI[7], **M. E. HILDEBRAND**[2];
[2]Carleton Univ., [1]Carleton Univ., Ottawa, ON, Canada; [3]Univ. of Ottawa, Ottawa, ON, Canada; [4]SickKids, Univ. of Toronto, Toronto, ON, Canada; [5]Eli Lilly & Co., Eli Lilly & Co., Indianapolis, IN; [6]Eli Lilly and Co., Carmel, IN; [7]Ottawa Hosp., Ottawa Hosp., Ottawa, ON, Canada

Abstract: Excitatory glutamatergic NMDA receptors (NMDARs) are key regulators of spinal pain processing, and yet the biophysical properties of NMDARs in dorsal horn nociceptive neurons remain poorly understood. Despite the clinical implications, it is unknown whether the molecular and functional properties of NMDAR synaptic responses are conserved between males and females as well as from rodents to humans. To address these translational gaps, we systematically compared individual and averaged excitatory synaptic responses from lamina I pain-processing neurons of adult Sprague Dawley rats and human organ donors, including both sexes. By combining patch-clamp recordings of outward miniature excitatory postsynaptic currents with non-biased data analyses, we uncovered a wide range of decay constants of excitatory synaptic events within individual lamina I neurons. Decay constants of quantal synaptic responses were distributed in a continuum from 1-20 ms to greater than 1000 ms, suggesting that individual lamina I neurons contain AMPA receptor (AMPAR)-only as well as GluN2A-, GluN2B-, and GluN2D-NMDAR-dominated synaptic events. This intraneuronal heterogeneity in AMPAR- and NMDAR-mediated decay kinetics was observed across sex and species. However, we discovered a decreased relative contribution of GluN2B-dominated NMDAR responses as well as larger amplitude GluN2D-like events at human lamina I synapses compared to rodent synapses, suggesting species differences relevant to NMDAR subunit-targeting therapeutic approaches. The conserved heterogeneity in decay rates of excitatory synaptic events within individual lamina I pain-processing neurons may enable synapse-specific forms of plasticity and sensory integration within dorsal horn nociceptive networks.

Disclosures: **A. Dedek:** None. **E. Topcu:** None. **C. Dedek:** None. **J.S. McDermott:** A. Employment/Salary (full or part-time):; Eli Lilly. **J.L. Krajewski:** A. Employment/Salary (full or part-time):; Eli Lilly. **E.C. Tsai:** None. **M.E. Hildebrand:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.21/C43

Topic:

Support: Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: N-glycosylation is a modulator of Kv3.4 ion channel kinetics

Authors: *E. LOGETTE[1,2], R. RANJAN[1], M. HERZOG[1], E. SCANTAMBURLO[1], M. JOFFRAUD[1], H. MARKRAM[1];
[1]BBP, Geneve, Switzerland; [2]Blue Brain Project, Campus Biotech, Ecole polytechnique fédérale de Lausanne, 1202 Geneva, Switzerland

Abstract: In mammals, eighty percent of membrane proteins, such as ion channels, are modified by N-glycosylation, which ensures their correct folding and localization at the plasma membrane, and in the case of ion channels, may affect their gating properties. In a previous study, we identified that certain voltage-gated potassium channels, like Kv3.4, display a wide range of kinetics under overexpression in a heterologous system, even under standardized conditions. In the current study, we have discovered that the kinetic heterogeneity of Kv3.4 is linked to its N-glycosylation status, directly influenced by glucose availability, and in a reversible manner. We also found that the kinetics of some of the other Kv channels are affected by their N-glycosylation status. These findings suggest that N-glycosylation could be a universal mechanism for modulating ion channel kinetics. Consequently, glucose metabolic disturbances could significantly impact the electrical properties of excitable cells in the brain, heart and other organs, which could explain some of the neurological defects observed in such metabolic diseases.

Disclosures: E. Logette: None. **R. Ranjan:** None. **M. Herzog:** None. **E. Scantamburlo:** None. **M. Joffraud:** None. **H. Markram:** None.

Poster

PSTR066. Other Ion Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR066.22/C44

Topic: B.03. Ion Channels

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology.

Title: Temperature-dependent kinetic characterization of all voltage-gated ion channels

Authors: *R. RANJAN[1], E. LOGETTE[2], K. H. ARULKANDARAJAH[2], M. HERZOG[2], S. V. DORP[2], E. SCANTAMBURLO[2], M. JOFFRAUD[2], H. MARKRAM[2];
[1]Blue Brain Project, Brain Mind Institute, EPFL, Lausanne, Switzerland; [2]Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL), Campus Biotech, Geneva, Switzerland

Abstract: Voltage-gated ion channels (VGICs) are integral membrane proteins that allow the flow of ions across the cell membrane, playing a crucial role in generating and transmitting electrical signals in excitable cells like neurons and muscle cells. Experimental characterization of their biophysical properties and voltage dependence primarily relies on voltage-clamp

electrophysiology experiments, which are essential for constructing accurate mathematical models of VGICs. Over the past four decades, there has been extensive research conducted to explore the molecular, structural, and biophysical properties of ion channels. However, characterizations of ion channel kinetics have focused on a few channels studied under widely varying experimental conditions, in different expression systems, with various manipulations, and mostly at unphysiological temperatures, resulting in a lack of standardized kinetic data for VGICs. Additionally, the absence of publicly-available raw experimental data further compounds this issue. To address this gap, we started with the kinetic characterization of 40 voltage-gated potassium channels in a study published in 2019 (Ranjan et al., 2019). Today, in this study, we present a comprehensive and systematic characterization of the biophysics of all major voltage-gated ion channels, encompassing Kv, K2P, Kir, KCa, Nav, Cav, and HCN channels in heterologous systems. Employing an automated patch-clamp system within a highly standardized workflow, we obtained temperature-dependent biophysical data on VGICs that were previously absent from the literature. Notably, our findings significantly deviate from the commonly reported data obtained at room temperature, highlighting the need for more comprehensive and standardized investigations in ion channel physiology and pathophysiology, particularly near physiological temperatures.

Disclosures: **R. Ranjan:** None. **E. Logette:** None. **K.H. Arulkandarajah:** None. **M. Herzog:** None. **S.V. Dorp:** None. **E. Scantamburlo:** None. **M. Joffraud:** None. **H. Markram:** None.

Poster

PSTR066. Other Ion Channels

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Topic: B.03. Ion Channels

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Title: Impaired interneuron excitability in a novel mouse model of epileptic encephalopathy due to the recurrent Kcnc1-p.Ala421Val variant

Authors: *M. A. CHENG[1], E. R. WENGERT[2], E. M. GOLDBERG[2,3,4];
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Abstract: The *KCNC1* gene encodes the voltage-gated potassium channel subunit $K_V3.1$, selectively expressed in fast-spiking GABAergic parvalbumin-positive interneurons (PV-INs). The recurrent c.1262C>T (p.Ala421Val or A421V) variant has been identified in patients presenting with developmental and epileptic encephalopathy (DEE). *KCNC1*-related epilepsy is without targeted treatment or cure, and the mechanisms whereby disease-associated variants induce pathology are not well understood. The $K_V3.1$-A421V variant has been shown to exhibit near-complete loss of function with dominant-negative action. We performed patch-clamp electrophysiology in PV-INs and pyramidal cells from acute brain slices prepared from male and female wild-type (WT) mice and a novel model of *KCNC1* epilepsy (*Kcnc1*-A421V/$^+$ mice) aged postnatal day (P) 16-21 to gain insight into how $K_V3.1$ deficiencies give rise to impaired inhibition, circuit-level hyperexcitability, and seizure activity. Whole-cell recordings identify several differences in the intrinsic physiology of PV-INs from WT mice and PV-INs from *Kcnc1*-A421V/$^+$ mice. Compared to WT, *Kcnc1*-A421V/$^+$ PV-INs have a significantly prolonged action potential half-width and action potential duration at 50% of repolarization along with a significantly slower downstroke velocity, properties consistent with K_V3 channel dysfunction. *Kcnc1*-A421V/$^+$ PV-IN steady-state firing frequencies for current injections at or above 200 pA decreased relative to WT, as did maximal instantaneous and steady-state firing frequencies. Outside-out voltage-clamp macropatch recordings reveal *Kcnc1*-A421V/$^+$ PV-INs have a significantly lower maximum K^+ current than WT PV-INs. Multiple whole-cell recordings of PV-INs and pyramidal cells indicate limited effects of *Kcnc1*-A421V/$^+$ on synaptic properties, suggesting the variant primarily mediates seizure activity through its impact on the excitability of PV-INs. We propose that the *Kcnc1*-A421V/$^+$ variant results in a major reduction of K_V3 current density, leading to impairment in the firing of fast-spiking GABAergic PV-INs. This in turn may lead to insufficient levels of synaptic inhibition, thereby causing neural circuit hyperexcitability. Together, these findings implicate PV-INs as a therapeutic target in *KCNC1*-related epileptic pathologies.

Disclosures: **M.A. Cheng:** None. **E.R. Wengert:** None. **E.M. Goldberg:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.01/C46

Topic: B.05. Synaptic Plasticity

Support: Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Acetylcholine redistributes synaptic efficacy in neocortical microcircuitry

Authors: *B. KOVACS[1], Y. SHI[2], R. PERIN[1], H. MARKRAM[1];
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Lausanne, Switzerland; [2]Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL), Campus Biotech, Geneva, Switzerland

Abstract: Neurons in the central nervous system (CNS) abundantly express acetylcholine (AChR) receptors, whose function is well characterized but not completely.A precise understanding of how ACh regulates local synaptic transmission to reconfigure global brain states is still lacking. Here, we investigated the excitatory-inhibitory (E-I) modulation of postsynaptic potentials (PSP) with paired patch clamp recordings from synaptically coupled neurons in mouse primary somatosensory cortex in layers 4 and 5 (L4/5) in acute mouse brain slices.We found that the presence of ACh reduces the EPSP transmission amplitude, however, IPSPs behaved differentially according to the presynaptic cell-type and the concentration of ACh. Lower concentrations of ACh decreased slightly the IPSP amplitude, whereas higher levels of ACh enhanced it significantly and the higher amplitude was maintained after wash out. Interestingly, a similar set up of experimental treatment with adenosine A1 receptor activation showed analogous responses in EPSPs (Sara et al., 2019). Moreover, our IPSP results are different than previously described in rat L1 neurogliaform (NGF) cell connections with L2/3 principal neurons (Arne et al., 2014) and distinct as it reported in L5 (Yamamoto et al., 2010).Our results highlight the many diverse neuromodulating effects of ACh in brain circuits.

Disclosures: B. Kovacs: None. **Y. Shi:** None. **R. Perin:** None. **H. Markram:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.02/C47

Topic: B.05. Synaptic Plasticity

Support: BRAIN Initiative F32: 5F32MH125582

Title: Presynaptic calcium activity drives heterogeneous dopamine-dependent plasticity in individual boutons of the Drosophila mushroom body

Authors: *A. M. DAVIDSON[1,2,3], S. KAUSHIK[1], T. HIGE[1,2,3];
[1]Biol., [2]Cell Biol. and Physiol., [3]Integrative Program for Biol. and Genome Sci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The *Drosophila* mushroom body (MB) is an important model system for studying the synaptic mechanisms of associative learning. In this system, coincidence of odor-evoked calcium influx and dopaminergic input in the presynaptic terminals of Kenyon cells (KCs), the principal neurons of the MB, triggers long-term depression (LTD), which plays a critical role in olfactory learning. However, it is controversial whether such synaptic plasticity accompanies a corresponding decrease in odor-evoked calcium activity in the KC presynaptic terminals. Here, we address this question by inducing LTD by pairing odor presentation with optogenetic activation of dopaminergic neurons (DANs). This allows us to rigorously compare the changes at

the pre- and postsynaptic sites in the same conditions. By imaging presynaptic acetylcholine release in the condition where LTD is reliably observed in the postsynaptic calcium signals, we show that neurotransmitter release from KCs is depressed selectively in the MB compartments innervated by activated DANs, demonstrating the presynaptic nature of LTD. However, total odor-evoked calcium activity of the KC axon bundles does not show concurrent depression. We further conduct calcium imaging in individual presynaptic boutons and uncover the highly heterogeneous nature of calcium plasticity. Namely, only a small subset of boutons, which are strongly activated by associated odors, undergo consistent calcium activity depression, while weakly responding boutons show considerably variable changes and even tend to show potentiation. Thus, our results suggest an unexpected nonlinear relationship between presynaptic calcium influx and the results of plasticity, challenging the simple view of cooperative actions of presynaptic calcium and dopaminergic input.

Disclosures: **A.M. Davidson:** None. **S. Kaushik:** None. **T. Hige:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.03/C48

Topic: B.05. Synaptic Plasticity

Support: NSERC RGPIN 2020 06757

Title: The influence of ovarian hormones on synaptic plasticity induced via repetitive transcranial magnetic stimulation

Authors: *K. R. RAMDEO, F. C. ADAMS, M. C. CUIZON, S. D. FOGLIA, F. FARAHMAND, A. J. NELSON;
McMaster Univ., Hamilton, ON, Canada

Abstract: Synaptic plasticity is fundamental to preserving and creating memories. In humans, synaptic plasticity can be assessed in vivo by delivery of Repetitive Transcranial Magnetic Stimulation (rTMS) in forms such as intermittent theta burst stimulation (iTBS) and 5Hz rTMS. Both patterned forms of stimulation delivered over the motor cortex can induce synaptic plasticity, which can be measured as short-term increases in the strength of the corticospinal pathway from the motor cortex to muscle. Ovarian hormones, namely estradiol and progesterone, play a crucial role in mediating plasticity. Estradiol affects learning and memory by influencing glutamate related processes, lowering neuron firing threshold, and promoting cortical excitability. Conversely, progesterone increases $GABA_A$ activity, reducing cortical excitability and leading to decreased motor evoked potential responses. There is evidence that indicates that ovarian hormones alter the response to rTMS. Females exhibit an increased response to 5Hz rTMS when estradiol levels are high, and a diminished response when estradiol levels are low. The effects of ovarian hormone levels on the response to iTBS and sham rTMS have yet to be

investigated. The goal of the research was to determine whether ovarian hormone levels modulate responses to iTBS induced synaptic plasticity in healthy female participants. It was hypothesized that individuals would show a greater propensity for plasticity during their follicular phase due to elevated levels of estradiol. Thirty adult females with regular menstrual cycles of approximately 28 days, participated in three sessions corresponding to the follicular phase, luteal phase, and a randomly selected day. Individuals were anonymized to the type of stimulation, iTBS or sham iTBS, delivered to their left motor cortex. During the randomly selected visit individuals received sham rTMS over the left motor cortex. Eighty motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle before and following iTBS. MEPs were acquired at 90, 110, 130, and 150% of the resting motor threshold of the FDI muscle. Results demonstrate that the greatest propensity for plasticity occurred during the follicular phase compared to the luteal phase and randomly selected visit. These findings suggest women experience a variable propensity for plasticity determined in part by fluctuations in ovarian hormones. This research proposes that therapeutic interventions using non-invasive brain stimulation should be administered during the follicular phase of the menstrual cycle in females to maximize the opportunity for synaptic plasticity.

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Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR067.04/C49

Topic: B.05. Synaptic Plasticity

Support: P30 DA013429
R01 DA043988
T32 DA007237

Title: Neuronal plasticity in the nucleus accumbens associated with cocaine contextual memory recall

Authors: *R. E. PRICE, R. P. FORTUNA, C. CABAN RIVERA, E. M. UNTERWALD;
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Abstract: Addiction is a disease associated with maladaptive learning and memory. In response to cocaineintoxication, reward pathways, including the nucleus accumbens, become inundated with dopaminewhich drives motivational and reinforcement learning. Repeated bouts of cocaine intoxication establishstrong memory traces. Persistent memories of drug intoxication associated with specific environmentalcues drive drug-seeking behaviors and hinder abstinence. This study aimed to investigate neuralplasticity in cells activated by recall of cocaine contextual memories. Using a conditioned placepreference paradigm, cocaine contextual memories were established in

male and female FosTRAP2-Ai14mice. Cocaine memory recall was achieved by re-exposure to the cocaine-paired context, whereascontrols remained in the home cage (no memory reactivation). 4-Hydroxytamoxifen was administeredduring memory recall to 'TRAP'and label activated Fos+ neurons with TdTomato (TdT). Brain sectionswere immunostained and imaged. TdTomato+ cell counts were quantified in FIJI (ImageJ). Individualmedium spiny neurons were captured with Nikon A1R confocal microscope and were imported forreconstruction and analysis using Neurolucida 360 and Explorer software. The reconstructed neuronaltraces were analyzed using the automated kernels method, to determine dendritic spine volume, headdiameter, neck diameter, density, and spine morphology (e.g., stubby, thin, mushroom, or filopodia).Sholl analysis was performed for dendritic branching. Results demonstrate that compared with homecage controls, recall of cocaine contextual memories significantly increased the number of activatedcells (TdT+) in the nucleus accumbens core and shell regions. Analysis of dendritic spines of mediumspiny neurons indicated significant morphological changes following recall of cocaine contextualmemories compared to home-cage controls. Significant increases in spine density were driven by anincrease in thin spines. Increase in spine surface area and reductions in the spine head and neckdiameter were found. Sholl analysis demonstrated a greater number of intersections and total dendritelength after cocaine memory recall compared to non-memory reactivated controls. These findingssupport the presence of neuronal plasticity in dendrites of activated medium spiny neurons within thenucleus accumbens following recall of cocaine contextual memories.

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Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.05/C50

Topic: B.05. Synaptic Plasticity

Support: CRC 1286 Quantitative Synaptology
Cluster of Excellence Multiscale Bioimaging

Title: Neuromodulation of the endbulb of Held to Bushy Cell synapse in the anteroventral cochlear nucleus by serotonin and norepinephrine

Authors: *T. ALVANOS[1], M. GROSHKOVA[2], T. MOSER[3];
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Abstract: Sound localization is crucial for the survival of a multitude of species and relies on the accurate representation of sound's temporal features in the lower auditory pathway. These

features are captured by time-coding neurons of the anteroventral cochlear nucleus (AVCN), the Bushy Cells (BCs). Large, calyceal synapses called endbulbs of Held arise from auditory nerve fibers (ANFs) and terminate onto the somata of BCs. There, hundreds of glutamate-filled synaptic vesicles (SVs) have a high release probability (P_r), thus generating supra-threshold postsynaptic currents (EPSCs). BCs encode the timing of acoustic stimuli allowing downstream neurons to distinguish very small differences in the time of sound arrival between the two ears. While tuned for fidelity, endbulbs display surprising variability of evoked release, but also convergent short-term plasticity (STP), whereby endbulbs converging on the same BC deplete their SV pools similarly. Monoaminergic modulation of the large endbulb of Held terminals by Norepinephrine (NE) and Serotonin (5-HT) is a promising candidate mechanism for tuning synaptic transmission and its variability. We labelled mouse AVCN slices against 5-HT - and NE transporters, revealing chains of varicosities likely releasing 5HT and NE in the AVCN. We performed further stainings to find which monoaminergic receptors, localized on the endbulb or BC membranes are juxtaposed to these varicosities. We voltage clamped mouse BCs from acute brainstem slices at physiological temperature and recorded miniature EPSCs (minis) and evoked EPSCs before and after bath - application of 5-HT or NE. The exposure to neuromodulators caused mild shifts in the kinetics of minis, as well as changes in STP, P_{vr} and recovery from readily releasable pool depletion compared to controls. In current clamp we recorded endbulb evoked BC action potentials, looking for firing latency changes upon exposure to neuromodulation. The endbulbs of Held provide a unique opportunity to understand presynaptic neuromodulation and changes in the equilibrium of SV docking, priming, fusion and endocytosis. By altering these processes or the excitability of postsynaptic BCs, neuromodulators may affect how temporal information is processed in the lower auditory pathway in the context of different behavioural states.

Disclosures: **T. Alvanos:** None. **M. Groshkova:** None. **T. Moser:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.06/C51

Topic: B.05. Synaptic Plasticity

Support: NRF-2019M3E5D2A01058328
MOTIE-20012355
NRF-2021M3E5D2A01019544

Title: The effect of inhibitory short-term plasticity on the propagation of spike synchrony in a feedforward network model

Authors: *J. YANG, J. KWAG;
Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The synchronization of precisely timed spikes among neurons is believed to carry information in neural networks. Many studies have shown that inhibitory inputs from GABAergic interneurons facilitate the synchronization of spike times. Especially, learning-induced modifications in synaptic weights and kinetics of inhibitory inputs, characterized by short-term plasticity (STP), have been reported in many neural circuits. However, the effects of different dynamics of STP, namely short-term depression (STD) and short-term facilitation (STF), on the synchronization of spike times remain elusive. To address this issue, we constructed a three-layer feedforward network (FFN) consisting of Hodgkin-Huxley-type excitatory (EX) and inhibitory (IN) neuronal models. The INs in each layer provided inhibition to EX at the IN-to-EX synapse through two distinct inhibitory neural circuit motifs, feedforward inhibition (FFI) and feedback inhibition (FBI), that showed either STD or STF or no STP. In response to different frequencies of synchronized spikes as inputs to the FFN model (5 - 80 Hz), FFN model with STD at the IN-to-EX synapse promoted spike synchrony at input spike frequency above 20 Hz in gamma frequency range, while FFN model with STF at the IN-to-EX synapse promoted spike synchrony below 20 Hz in the theta, alpha and beta frequency range. Together, our results suggest that different STP types dynamically promote frequency-selective propagation of spike time synchronization, indicating that modification in learning-induced changes in STP may dynamically gate the neural synchrony in the neural network.

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Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.07/C52

Topic: B.05. Synaptic Plasticity

Support: Weston Brain Institute

Title: Does priming the brain with transcranial alternating current stimulation benefit the transcranial magnetic stimulation?

Authors: *M. A. UEHARA[1], Z. MOUSSAVI[2];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation being researched as a potential treatment for other neurological disorders. Preconditioning the brain with transcranial alternating current stimulation (tACS) prior to rTMS may increase cortical excitability, thereby reducing the required exposure for neuronal activation. People with a high minimum resting motor threshold (RMT) values who may have difficulty tolerating rTMS scalp sensations would benefit from using a technique (e.g. priming with tACS) to reduce RMT. In this study, 6 participants (2 males) with no cognitive impairment were recruited. Their minimum RMT was determined using electromyography of the first dorsal

interosseous muscle and abductor pollicis brevis and a visible involuntary twitch. The participants' RMT was measured pre and post 10-min priming with tACS. The RMT changes with respect to pre-priming were measured over 1 hour period (right after, 30 min after, and 1 hour after). Precise localization of coil positioning for each RMT measurement was performed using neuronavigation. The tACS electrodes were applied over the left and right hand area motor cortex with sponge electrodes for 10 min at 40 Hz with 0.75 mA peak-to-peak. Repeated measures ANOVA determined that there was statistically significant differences at different time points of MEP ($F(3, 15) = 8.077$, $p = 0.002$). Assumptions of normality, sphericity, and no significant outliers were confirmed. Normality was evaluated using Shapiro-Wilk test ($p > 0.05$) and spherecity with Mauchly's test ($p > 0.05$). Post-hoc analysis showed MEP increases at immediately and 30-min after tACS priming compared to baseline were statistically significant ($p < 0.031$) by a mean difference of 32.25 μV, and 53.65 μV, respectively. After 1 hour of tACS priming, there was no significant difference in MEP compared to baseline ($p = 0.381$). Despite the significant changes in MEP, there was no significant difference in RMT values between pre and post tACS priming at any time period of measurement; the changes were within 1-2% compared to baseline. In conclusion, tACS at 40 Hz for 10 min provides minimal increase in cortical excitability as seen by the increase in MEP for approximately 30 min after 10 min of tACS. However, tACS does not significantly decrease RMT to provide easier administration of rTMS for people with high RMT values.

Disclosures: M.A. Uehara: None. **Z. Moussavi:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.08/C53

Topic: B.05. Synaptic Plasticity

Support: R37NS045876

Title: The role of Bcl-xL in regulating presynaptic vesicle pools

Authors: *S. SUBRAMANIAN[1], S. SACCHETTI[2], S. WATANABE[3], H.-A. PARK[4], P. LICZNERSKI[1], C. PAN[1], M. HARDWICK[3], V. GRIBKOFF[1], E. A. JONAS[1];
[1]Yale Univ. Sch. Med., New Haven, CT; [2]Inst. Italiano di Tecnologia, Genova, Italy; [3]Johns Hopkins Univ., Baltimore, MD; [4]Univ. of Alabama, Tuscaloosa, AL

Abstract: Synaptic plasticity involves a change in the magnitude of response to a given stimulus. This change is initiated by a pattern of stimulation of the presynaptic neuron, which in presynaptic plasticity leads to an increase or decrease in the amount of neurotransmitter released by this neuron. During short-term plasticity, an increase in the size of the readily releasable pool (RRP) of vesicles corresponds to an enhanced post-synaptic response to stimulation. The cell survival protein Bcl-xL alters the presynaptic landscape by increasing the number and size of

presynaptic vesicle clusters as well as by recruiting mitochondria to the presynaptic terminal. Bcl-xL also increases the efficiency of mitochondrial ATP production, thereby fueling aspects of the energy-demanding process of synaptic transmission. Bcl-xL forms a complex with Drp-1 to aid with endocytosis of vesicles following neurotransmitter release, which is critical to replenishing presynaptic vesicle pools. Less is understood about the role of Bcl-xL in exocytosis. Here, we inhibited Bcl-xL with the specific small-molecule inhibitors ABT-737 and WEHI-539 to explore the role of Bcl-xL in presynaptic neurotransmitter release in hippocampal synapses. Bcl-xL inhibition led to a reduction in the re-accumulation of vesicles in the presynaptic terminal following stimulation as well as a decrease in the size of the RRP. Instead of vesicles re-accumulating at the plasma membrane, Bcl-xL inhibition led to an increase in the size of presynaptic endosomes, suggesting that vesicles were not being fully recycled to the RRP. We recently found that Bcl-xL inhibition increases the likelihood of vesicle transport to lysosomes for degradation following endocytosis, suggesting that Bcl-xL may coordinate information about synaptic activity with cellular metabolic state to adjust the size of the RRP. Together, vesicle recycling and enlargement of the RRP act to increase the amount of neurotransmitter released by the presynaptic terminal following stimulation.

Disclosures: **S. Subramanian:** None. **S. Sacchetti:** None. **S. Watanabe:** None. **H. Park:** None. **P. Licznerski:** None. **C. Pan:** None. **M. Hardwick:** None. **V. Gribkoff:** None. **E.A. Jonas:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.09/C54

Topic: B.05. Synaptic Plasticity

Support: Department of Atomic Energy, Govt of India, Project ID RTI 4006

Title: Short-term Plasticity of E-I Balance in Hippocampal CA3-CA1 circuit probed using Patterned Stimulation

Authors: *A. ASOPA, U. S. BHALLA;
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Abstract: Hippocampal CA3-CA1 circuit represents multiple modalities including time, space, and orientation. It shows precise balance of excitation and inhibition (Bhatia et al 2019). When excitation at CA1 is increased the inhibitory inputs also increase proportionately, thus balancing the depolarization. But for CA1 cells to represent information, they must cross the threshold and fire. We study how the precise E-I balance in CA1 pyramidal neurons evolves with changing firing rates in CA3 layer cells, resulting in action potentials.
We performed in vitro whole cell patch clamp recordings from CA1 cells in acute mouse hippocampal sections (male and female, 2-3 months of age). We simultaneously stimulated

Channelrhodopsin (ChR2) expressing CA3 pyramidal cells with 13um x 8um spots using a sub-cellular-resolution patterned projection (Mightex Polygon 400). We created 5-spot and 15-spot patterns from a set of 45 spots. These patterns were used to stimulate CA3 cells at multiple frequencies (8 pulses at 20, 30, 40, 50, and 100Hz).
We measured excitatory and inhibitory currents in voltage clamp and responses of the CA1 cells in current clamp. As a control we also blocked inhibition using Gabazine. A synaptically detailed circuit model was built using the voltage clamp data that was used to predict the spiking behavior of CA1 cells under various protocols.
We observed that inhibition blocks excitation for the entire duration of the pulse train preventing the receiving cell from firing. At lower frequencies, excitation undergoes short-term potentiation first and followed by short-term depression. On the other hand, dysynaptic inhibition follows short-term depression for all frequencies tested. Thus the receiving CA1 neurons have the highest E-I ratio in the early part of a train before the combined effects of STP of E and I synapses, cause insufficient depolarization for crossing the threshold. Thus when inhibition is blocked, for stronger stimuli, (15sq) the cells fire in the first pulse, while weaker stimuli (5sq) fire in second or third pulse.
Using the model trained on the recordings, we aim to predict spiking behaviour of the CA1 cells under invivo like activity patterns in CA3.
Finally, we propose that E-I dynamics may play an important role in gating and recruitment of neuronal ensembles in place or time cell sequences.

Disclosures: **A. Asopa:** None. **U.S. Bhalla:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.10/C55

Topic: B.04. Synaptic Transmission

Title: Endogenous Opioid Signaling within the Paraventricular Nucleus of the Thalamus

Authors: *S. SHIRLEY, M. A. PENZO, H. A. TEJEDA;
NIMH, NIH, Bethesda, MD

Abstract: An organism’s survival depends on its ability to integrate and respond to emotional and homeostatic signals. The paraventricular nucleus of the thalamus (PVT) functions as an integrative hub for these signals, with strong innervation from inputs conveying internal state, arousal, and stimuli salience. The PVT can shape behavioral responses to homeostatic challenges through divergent projections to various limbic regions, such as the nucleus accumbens (NAc), central nucleus of the amygdala (CeA), and medial prefrontal cortex (mPFC). Current research has shown that the PVT is heterogeneous across its antero-posterior axis. There is diverse expression of neuromodulatory receptors that may allow for information to be communicated from PVT inputs to a select subset of PVT cells and regulate distinct motivational and emotional

behaviors. One set of receptors expressed across the PVT implicated in these behaviors are the inhibitory kappa- (KOR) and mu-opioid receptors (MOR), which are preferentially activated by the endogenous opioid ligands dynorphin (Dyn) and enkephalin (Enk). KOR and MOR have been implicated in negative affective behaviors and reward function, respectively. However, how functional KOR and MOR integrate into PVT cellular heterogeneity to drive behavioral responses is relatively unknown. Using patch-clamp electrophysiology, we show that Dyn signaling preferentially inhibits anterior PVT cells, relative to posterior PVT cells. We also find that Dyn inhibits virtually all NAc- projecting neurons, approximately half of CeA-projecting cells robustly, and a small population of mPFC projecting cells, suggesting that Dyn may differentially suppress activity in distinct PVT outputs. In contrast, Enk signaling has less of a topographical bias (anterior to posterior) but most strongly targets CeA projectors, demonstrating that Enk and Dyn may differentially modulate PVT circuits. Ongoing work is aimed at identifying and characterizing the Dyn and Enk inputs to the PVT. Using a combination of viral circuit tracing, in situ hybridization and electrophysiology, we will identify the sources of Dyn and Enk, the neurotransmitters they are co-released with, and how the inclusion of Dyn and Enk in the mixture of signals alters how PVT neurons integrate information and signal to outputs. This work provides a foundation for us to elucidate how endogenous opioids regulate homeostatic and emotional processing at the cellular level. Understanding the fundamentals of PVT signal integration will provide a mechanism to describe how the motivated behaviors and emotions essential for survival are driven by homeostatic and environmental challenges.

Disclosures: S. Shirley: None. **M.A. Penzo:** None. **H.A. Tejeda:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.11/C56

Topic: B.04. Synaptic Transmission

Support: ZIA MH002970-04
CCB from HEY
NARSAD Young Investigator Award from HT

Title: Dynorphin / kappa-opioid receptor regulation of excitation-inhibition balance toggles afferent control of prefrontal cortical circuits in a pathway-specific manner

Authors: *H. E. YARUR, V. S. TSAI, S. CASELLO, J. ENRIQUEZ TRABA, H. WANG, M. ARENIVAR, H. A. TEJEDA;
NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: The medial prefrontal cortex (mPFC) controls behavior via connections with limbic excitatory afferents that engage various inhibitory motifs to shape mPFC circuit function. The dynorphin (Dyn) / kappa-opioid receptor (KOR) system is highly enriched in the mPFC, and its

dysregulation is implicated in neuropsychiatric disorders. However, it is unclear how the Dyn / KOR system modulates excitatory and inhibitory circuits that are integral for mPFC information processing and behavioral control. Here, we provide a circuit-based framework wherein mPFC Dyn / KOR signaling regulates excitation-inhibition balance by toggling which afferents drive mPFC neurons. Dyn / KOR regulation of afferent inputs is pathway-specific. Dyn acting on presynaptic KORs inhibits glutamate release from afferent inputs to the mPFC, including the basolateral amygdala (BLA), paraventricular nucleus of the thalamus, and contralateral cortex. The majority of excitatory synapses to mPFC neurons, including those from the ventral hippocampus (VH), do not express presynaptic KOR, rendering them insensitive to Dyn / KOR modulation. Dyn / KOR signaling also suppresses afferent-driven recruitment of specific inhibitory sub-networks, providing a basis for Dyn to disinhibit mPFC circuits. Specifically, Dyn / KOR signaling preferentially suppresses SST interneuron- relative to PV interneuron-mediated inhibition. Selective KOR action on afferents or within mPFC microcircuits gates how distinct limbic inputs drive spiking in mPFC neurons. Presynaptic Dyn / KOR signaling decreases KOR-positive input-driven (e.g. BLA) spiking of mPFC neurons. In contrast, KOR-negative input recruitment of mPFC neurons is enhanced by Dyn / KOR signaling via suppression of mPFC inhibitory microcircuits. Thus, by acting on distinct circuit elements, Dyn / KOR signaling shifts KOR-positive and negative afferent control of mPFC circuits, providing mechanistic insights into the role of neuropeptides in shaping mPFC function. Together, these findings highlight the utility of targeting the mPFC Dyn / KOR system as a means to treat neuropsychiatric disorders characterized by dysregulation in mPFC integration of long-range afferents with local inhibitory microcircuits.

Disclosures: H.E. Yarur: None. **V.S. Tsai:** None. **S. Casello:** None. **J. Enriquez Traba:** None. **H. Wang:** None. **M. Arenivar:** None. **H.A. Tejeda:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.12/C57

Topic: B.04. Synaptic Transmission

Support: ZIA MH002970-04
NARSAD Young Investigator Award
NIH Center for Compulsive Behaviors Fellowship

Title: Regulation of prefrontal cortex interneuron function by enkephalin signaling through mu- and delta-opioid receptors

Authors: *V. S. TSAI, H. E. YARUR, H. WANG, H. A. TEJEDA;
NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: The medial prefrontal cortex (mPFC) is crucial for the orchestration of goal-directed behavior and executive function, a process which is disrupted in many neuropsychiatric conditions. Dysfunction in opioidergic neurotransmission has also been implicated in neuropsychiatric disorders. Endogenous opioids and their receptors are highly expressed in the mPFC of humans and rodents, but the neurophysiological mechanisms underlying opioidergic modulation of mPFC circuitry are not well understood. Here, we used *in-situ* hybridization and whole cell patch-clamp electrophysiology to characterize the role of enkephalin (ENK) actions on mu- and delta-opioid receptors (MOR and DOR) in shaping mPFC circuitry. *In-situ* hybridization results reveal that mPFC ENK and MOR and/or DOR mRNA-expressing cells segregate into non-overlapping neuronal subpopulations. ENK mRNA was expressed by excitatory and inhibitory neurons, the latter of which were primarily VIP-positive interneurons lacking MOR or DOR mRNA. MOR mRNA was robustly expressed in SST-positive interneurons, while DOR mRNA was biased towards PV-positive interneurons. Electrophysiological recordings from GABAergic interneurons corroborated these findings, demonstrating that ENK signaling through MOR and/or DOR inhibited interneurons based on electrophysiological signatures. Further characterization of these interneuron subpopulations using principal components analysis and hierarchical clustering revealed distinctive clusters of fast spiking and non-fast spiking interneurons with selective responsivity to DOR agonist or MOR agonist, respectively. Many cells responded to both MOR and DOR agonists and a subset responded to neither, supporting the hypothesis that MOR/DOR expression converges in certain interneuron sub-populations and not others. Preliminary results disentangling potential signaling interactions in interneurons co-expressing MOR and DOR suggest the two receptors act on different fibers, synaptic compartments, and/or downstream effectors. Differential expression of MOR and DOR across interneuron subpopulations and synaptic compartments indicates ENK signaling through MOR and/or DOR inhibits interneurons in a subclass-specific manner. Together, these findings suggest that ENK signaling may participate in a disinhibitory microcircuit, wherein ENK release by VIP interneurons or pyramidal neurons suppresses interneurons through MOR and/or DOR activation. Inhibitory control of specific interneuron subpopulations by non-overlapping and co-expressing opioid receptors may be a mechanism by which opioids gate mPFC circuitry and executive control.

Disclosures: **V.S. Tsai:** None. **H.E. Yarur:** None. **H. Wang:** None. **H.A. Tejeda:** None.

Poster

PSTR067. Synaptic Transmission: Plasticity and Modulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.13/C58

Topic: E.07.a. Cellular properties – Interneurons and motor neurons

Support: DFG NI683- 13-1

Title: Contribution of glutamatergic and GABAergic mechanisms to the plasticity-modulating effects of dopamine in the human motor cortex

Authors: *E. GHANAVATI[1], M. SALEHINEJAD[2], L. DE MELO[3], M.-F. KUO[3], M. A. NITSCHE[3];
[1]Psychology and Neurosciences, Leibniz Res. Ctr. for working environment (ifado), Dortmund, Germany; [2]Psychology and Neurosciences, Leibniz-Institut fur Arbeitsforschung an der TU Dortmund, Dortmund, Germany; [3]Psychology and Neurosciences, Leibniz Res. Ctr. for working environment and Human Factors, Dortmund, Germany

Abstract: Dopamine (DA) has an impact on cortical excitability and plasticity which are core physiological components of cognition. These effects of DA depend on glutamate and GABA receptors, which are differentially affected DA receptor subtypes (D1, D2). Non-invasive brain stimulation techniques are suited to induce plasticity (via transcranial direct current stimulation-tDCS) and monitor cortical facilitation and inhibition (via transcranial magnetic stimulation-TMS). In this randomized, placebo-controlled double-blinded study, we explored the impact of DA, D1 and D2 receptor activation on tDCS-induced LTP/LTD-like plasticity induced by anodal and cathodal tDCS with respect to glutamatergic and GABAergic mechanisms. Eighteen healthy volunteers received 1 mA of anodal (13 min)and cathodal tDCS (9 min) over the left motor cortex combined with the dopaminergic agents L-Dopa (general DA activation), bromocriptine (D2 activation), the D2 antagonist Sulpiride+L-Dopa (D1 activation) and placebo. Glutamate-related cortical facilitation and GABA-related cortical inhibition were monitored with intracortical facilitation (ICF) and short-interval cortical inhibition (SICI) TMS protocols. Our results show that under placebo condition, anodal tDCS increased cortical facilitation and decreased inhibition while cathodal tDCS generated the opposite pattern of results. Under General DA activation, anodal tDCS did not change cortical inhibition and facilitation. However, cathodal tDCS increased and decreased cortical inhibition and facilitation respectively. Under D2 receptor activation, both anodal tDCS and cathodal tDCS decreased cortical facilitation and increased cortical inhibition. Finally, by D1 receptor activation, cortical inhibition and facilitation were increased after anodal tDCS while cathodal tDCS effects on these parameters were abolished. These results suggest while D1 activation enhanced the efficacy of anodal tDCS to increase cortical facilitation and decrease inhibition, it abolished LTD-like plasticity likely via enhanced glutamatergic activity. D2 activation had opposite effects on anodal tDCS-induced plasticity, and caused more inhibition, while it prolonged the inhibitory effects of cathodal tDCS possibly because of a reduction of glutamate activation.

Disclosures: E. Ghanavati: None. **M. Salehinejad:** None. **L. de Melo:** None. **M. Kuo:** None. **M.A. Nitsche:** F. Consulting Fees (e.g., advisory boards); Neuroelectrics.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.01/C59

Topic: B.05. Synaptic Plasticity

Support: ROIMH135565
ROINS118440

Title: The effect of post-learning sleep deprivation on neuronal activation, ensemble reactivation, and transcript expression in the mouse dentate gyrus

Authors: *K. O. MCDONALD, L. WANG, C. GONZALEZ, S. ATON;
MCDB, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Post-learning sleep deprivation (SD) disrupts hippocampal memory consolidation, including consolidation of contextual fear memory (CFM) in mice following contextual fear conditioning (CFC). This observed SD-induced memory deficit may result from disrupted neuronal ensemble reactivation. Areas of the hippocampus are heterogenous in structure and function and may respond differently to post-learning sleep or SD. Here we investigate the overall impact of post-learning sleep and SD on neuronal activity, neuronal ensemble reactivation, and transcript expression in the subregions of the mouse hippocampus. Analysis of neuronal activity markers in the hippocampi of male C57BL6 mice show that following a 6-h period of SD, neuronal activity is higher in the superior blade compared to the inferior blade of the dentate gyrus (DG). This effect is driven by significant reductions in neuronal activity in the inferior blade, but not the superior blade, following 3- or 6-h periods of SD. To understand how memory encoding-activated ensembles are reactivated in the hours following learning, we used targeted recombination of activated populations (TRAP) in male reporter mice to label context-specific neurons (engram cells) in the DG. We then quantified engram cells' reactivation after a period of sleep or SD. Animals allowed to sleep freely following learning exhibited a higher level of ensemble reactivation compared to animals that underwent 6 hours of post-learning SD. SD prevented this reactivation of engram cells in the inferior blade of DG. We did not observe significant ensemble reactivation, and thus no change in reactivation across subregions, in the 3-hour post learning mice after either sleep or SD. Transcript expression analysis demonstrated that 6-h SD led to differential expression of select transcripts in the DG inferior vs. superior blades, and in other hippocampal subregions, suggesting a significant and region-specific impact of sleep on gene expression. Transcripts associated with neuronal activity, protein synthesis regulation, synaptic signaling, and cytoskeletal remodeling were differentially affected in the DG blades (compared with other hippocampal subregions) following SD. Taken together, our results suggest that sleep plays an important role in regulating hippocampal DG activity, engram cell reactivation, and transcription in the hours following learning. These effects are subregion-specific, and likely contribute to memory consolidation.

Disclosures: K.O. McDonald: None. **L. Wang:** None. **C. Gonzalez:** None. **S. Aton:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.02/C60

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01 NS104776
NIH Grant RF1 NS118440
Rackham Merit Fellowship

Title: Bidirectional manipulation of orexinergic neurons show sexual dimorphism in learning and memory

Authors: *A. VEGA MEDINA[1], J. CHIU[2], J. N. NEELEY[2], M. HIRSCH[2], M. ELKOURI[1], S. J. ATON[1,2];
[1]Neurosci. Grad. Program, [2]Molecular, Cellular, and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: Sleep deprivation is thought to affect 30% of the population worldwide. Yet our understanding of how sleep disorders develop, how to treat them, and how to prevent cognitive impairment associated with lack of sleep remains limited. Previous studies from our lab have suggested that orexinergic inputs to the hippocampus are more active when mice are sleep deprived, but whether this plays a role in the mechanism for disruption of hippocampal memories during sleep deprivation is unknown. We have used excitatory and inhibitory chemogenetic manipulations to bidirectionally modulate orexin neurons' activity in the hours following learning, using two hippocampus-dependent, sleep-dependent tasks: contextual fear conditioning and object location memory. Our preliminary data suggest that the effects of these manipulations are both sex- and task-specific. To better understand these differences, we are using Brainbow viral tracing to assess whether there are morphological differences in orexinergic inputs to the hippocampus, and other brain structures, between males and females. These studies will test the hypothesis that sex differences in orexinergic circuitry may lead to sex differences in their contribution to behavior, memory consolidation, and sleep-wake regulation.

Disclosures: A. Vega Medina: None. **J. Chiu:** None. **J.N. Neeley:** None. **M. Hirsch:** None. **M. Elkouri:** None. **S.J. Aton:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.03/C61

Topic: B.05. Synaptic Plasticity

Support: NIA Training Grant AG000114

Title: State-dependent regulation of hippocampal memory consolidation via somatostatin interneurons

Authors: *V. BALENDRAN, S. J. ATON;
Univ. of Michigan, ANN ARBOR, MI

Abstract: We have recently found that sleep deprivation (SD) in the hours following single-trial contextual fear conditioning (CFC) selectively activates somatostatin-expressing (SST+) inhibitory interneurons in the hippocampus, while drastically reducing overall activity in the granule cell layer of the dentate gyrus. We propose a mechanism by which the SD-driven increase in SST+ interneuron activity downregulates activity in surrounding hippocampal principal neurons, such that contextual fear memory (CFM) consolidation is disrupted. While both the hippocampus and neocortex play critical roles in memory consolidation, it is unclear whether similar mechanisms affect SST+ interneurons in the neocortex in the context of sleep-dependent memory consolidation. Because the entorhinal cortex serves as an interface between the hippocampus and neocortex and is critical for memory consolidation and retrieval, we tested the effects of CFC and sleep-state on the activity and synaptic plasticity of SST+ interneurons. Using immunohistochemistry for cFos to assess entorhinal SST+ interneuron and principal neuron activation, we tested the hypothesis that post-learning sleep vs. SD differentially impacts the excitatory-inhibitory balance of this circuit. We also compared dendritic spine densities in SST+ interneurons in DG vs. entorhinal cortex after periods of post-CFC sleep vs. SD, using Brainbow labeling. These studies will assess how the input to DG is affected by learning and subsequent sleep. They will also provide important insight into the role of the entorhinal cortex as it relates to sleep and memory consolidation.

Disclosures: V. Balendran: A. Employment/Salary (full or part-time):; University of Michigan. **S.J. Aton:** A. Employment/Salary (full or part-time):; University of Michigan.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.04/C62

Topic: B.05. Synaptic Plasticity

Support: R01 MH135565
R01 NS118440

Title: Nrem-targeted activation of medial septal cholinergic input to hippocampus disrupts consolidation of multiple hippocampal-dependent memories

Authors: *D. MCKINSTRY[1], S. ATON[2];
[2]Molecular, Cell. & Developmental Biol., [1]Univ. of Michigan, Ann Arbor, MI

Abstract: Long-term memory consolidation is an indispensable hippocampal process, which can be obstructed by post-learning sleep disturbances. As the brain transitions from wakefulness to non-rapid eye movement (NREM) sleep to REM sleep, the hippocampus undergoes changes in both network activity and levels of neuromodulator release. For example, acetylcholine (ACh)

release in the hippocampus is lowest during NREM sleep and highest during REM sleep. Recent work from our lab has shown that chemogenetic activation of medial septum (MS) ACh input to the hippocampus immediately following contextual fear conditioning (CFC) is sufficient to decrease network activity in the dentate gyrus (DG) and disrupt contextual fear memory (CFM) consolidation. In contrast, chemogenetic inhibition of these inputs promotes DG activity and CFM consolidation. Together, this suggests that reduction of ACh release in the hippocampus during NREM sleep could be required for hippocampal memory consolidation. To test this, we measured effects of post-learning, NREM-specific optogenetic activation of MS ACh neurons on memory consolidation and *in vivo* electrophysiology. *ChAT-Cre* transgenic mice were transduced with a Cre-dependent AAV ChR2-eYFP expression vector and an optical fiber targeting MS, along with EEG and EMG electrodes to monitor sleep architecture and measure network activity during sleep states. Mice were trained on one of two different hippocampus-dependent memory tasks - object-location memory (OLM)or CFM, after which they were allowed *ad lib* sleep with or without optogenetic stimulation of MS ACh neurons targeted to bouts of NREM sleep over the first 6 h. NREM-targeted activation of MS ACh neurons disrupted consolidation of bothOLM and CFM, evaluated 24 h after training. While NREM-targeted MS stimulation had limited effects on either NREM or REM sleep architecture and EEG activity, it did disrupt the enhancement in sharp wave-ripple oscillations and amplitude that normally accompanies memory consolidation. Furthermore, NREM-targeted stimulation following CFC led to an increase in the number of cFos+ neurons present throughout the dentate gyrus (DG) after CFM recall, with increased numbers of DG hilar neurons negatively correlated with successful memory consolidation. These data suggest that suppression of ACh release in the hippocampus during post-learning NREM sleep is necessary for proper hippocampus-mediated memory consolidation, and may lead to network changes that balance activation patterns of excitatory and inhibitory neurons in the hippocampal DG network during recall.

Disclosures: D. McKinstry: None. **S. Aton:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.05/C63

Topic: B.05. Synaptic Plasticity

Support: R01MH107182
NCI CCSG P30 CA060553

Title: Visualizing AnkG-190 nanodomains in dendritic spines using expansion microscopy.

Authors: *N. H. PIGUEL, P. PENZES;
Neurosci., Northwestern Univ. - Feinberg Sch. of Med., Chicago, IL

Abstract: The ANK3 gene, encoding the protein ankyrin-G (AnkG), is associated with a variety of neuropsychiatric and cognitive disorders including bipolar disorder and autism spectrum disorder characterized by abnormal dendritic and synaptic architecture. AnkG is a multifunctional scaffold protein with several isoforms: the 480 kDa and 270 kDa isoforms have important roles at the axon initial segment and node of Ranvier whereas the function of the 190 kDa isoform (AnkG-190) appears more specialized in the dendritic area of glutamatergic neurons. We have previously described AnkG-190's roles in dendrite complexity and dendritic spine morphology and how its palmitoylation is essential to maintain its cellular localization and function. Moreover, the presence of AnkG-190 in the dendritic spine neck seems important for spine enlargement during Long Term Plasticity. In this work, we investigate AnkG-190 localization at a nanoscopic scale in the dendritic spine using expansion microscopy to understand how AnkG-190 localization plays a role in its different functions.

Disclosures: **N.H. Piguel:** None. **P. Penzes:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.06/D1

Topic: B.05. Synaptic Plasticity

Support: NIH Grant : 5R01MH097216-09
NIH Grant : 1R01NS100785-01A1

Title: A human CSF-based therapeutic strategy to improve brain function in a mouse model of psychiatric disorders

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Abstract: Cerebrospinal fluid (CSF) is essential for normal brain function and is a valuable source of biomarkers, due to its proximity to brain cells. However, it is still unclear how CSF proteins impact neuronal networks and brain function in both normal and pathological conditions. Here, we used discovery-based mass spectrometry to screen for alterations in CSF composition in schizophrenia, a common psychiatric disorder. We find that dysregulated CSF proteins are enriched in cortical genes and identified reduced levels of proteins originating from synapses. To better understand the role of CSF proteins on neuronal networks, we designed synthetic soluble synaptic proteins mimicking the same sequences observed in CSF. We found that the synthetic peptide preferentially binds to synapses located on inhibitory neurons, and exogenous application of the peptide increased inhibitory neuron activity, causing a reduction in

neuronal network activity in local cortical and hippocampal circuits. We investigated the potential therapeutic efficacy of synaptic CSF proteins, in a genetic mouse model of 16p11.2 duplication syndrome, a copy number variant associated with schizophrenia and neuropsychiatric disorders. Acute infusion of the synthetic protein in the prefrontal cortex of adult model mice was sufficient to restore wild-type levels of Parvalbumin expression and normal cognitive performance. Our work demonstrates that CSF synaptic proteins are cell-type specific network regulators, and highlights CSF synaptic proteins as a novel source of potential therapeutics for psychiatric disorders.

Disclosures: **M. Dos Santos:** None. **M. Forrest:** None. **E.K. Bomba-Warczak:** None. **E.L. Parnell:** None. **M. Martin-de-Saavedra:** None. **B.L. Eckman:** None. **M. Barbolina:** None. **J.N. Savas:** None. **P. Penzes:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.07/D2

Topic: B.05. Synaptic Plasticity

Support: KAKENHI 20H05903
KAKENHI22K21351
KAKENHI 23H02518A
KAKENHI 23H02663

Title: Synaptic plasticity in the prefrontal cortex causally regulates slow wave sleep in mice.

Authors: *Y. IINO[1,3], K. YOSHIDA[4,3], T. SAWADA[5,2], C. SHIMIZU[3], M. JUICHI[3], M. YANAGISAWA[3], T. SAKURAI[3], H. KASAI[5], **S. SHI**[3];
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Abstract: Synaptic strength in the cerebral cortex has been shown to fluctuate with the sleep-wake cycle. Empirical evidence suggests that synapses are primarily potentiated during wakefulness and downregulated during sleep, but current network models and single-neuron mathematical models do not posit that synaptic potentiation alone instigates sleep. Thus, the causal relationship between synaptic potentiation and sleep remains elusive. In this study, we investigated whether synaptic potentiation triggers sleep using a two-population mathematical model composed of excitatory and inhibitory neuronal populations. Our model demonstrates that synaptic potentiation between excitatory neurons could facilitate the transition from continuous to intermittent spiking activity by destabilizing up states, suggesting that synaptic potentiation amongst excitatory neurons may instigate the shift from sustained awake-like firing patterns to alternating up and down states (slow oscillations). Consistent with this prediction, systemic

administration of a positive allosteric modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which mimics long-term potentiation (LTP), increased non-rapid eye movement (NREM) sleep in mice. Additionally, pharmacological inhibition of long-term depression (LTD) increased NREM sleep. These results suggest LTP and LTD plays a significant role in sleep-wake regulation. Furthermore, we observed changes in the dendritic spine size through the sleep-wake cycle via histological analysis, suggesting a possibility that the sleep-wake cycle is orchestrated by the LTP-LTD cycle. To pinpoint the underlying mechanism, as well as the responsible brain regions and cell-type, we utilized a novel genetically encoded molecular tool to induce LTP (Sawada et al). This tool revealed that inducing LTP in the excitatory or inhibitory neurons of the prefrontal cortex (PFC) causally increased or decreased NREM sleep, respectively. Importantly, we also observed a concomitant change in the dendritic spine size within the PFC. Interestingly, inducing LTP in the visual cortex did not affect sleep, thereby highlighting the pivotal role of the PFC in sleep regulation. In conclusion, this study provides evidence of a causal relationship between synaptic potentiation in the PFC and NREM sleep regulation. Given that neuropsychiatric disorders such as depression and schizophrenia are often accompanied by sleep disturbances and abnormalities in the morphology of dendritic spines in the PFC, these spines represent an intriguing target for novel therapeutic interventions.

Disclosures: **Y. Iino:** None. **K. Yoshida:** None. **T. Sawada:** None. **C. Shimizu:** None. **M. Juichi:** None. **M. Yanagisawa:** None. **T. Sakurai:** None. **H. Kasai:** None. **S. Shi:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.08/D3

Topic: B.05. Synaptic Plasticity

Support: JST JPMJAX2116
KAKENHI 23K14285
KAKENHI 20H05685
JST JPMJCR21E2

Title: A chemogenetic tool for inducing synaptic potentiation

Authors: *T. SAWADA[1,2,3,4], H. OKAZAKI[2,3], T. ARIMA[3,2], Y. IINO[4], S. ZHOU[2], C. SHIMIZU[4], S. YAGISHITA[3,2], S. SHI[4], H. KASAI[2];
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Abstract: Dendritic spine enlargement and proportional increases in glutamate sensitivity have been considered the basis of learning and memory. Recently, several optical techniques have

been developed to induce the enlargement or shrinkage of spines. However, the investigation of the effects of synaptic changes on behavior has been challenging due to limitation in the number of targeted spines. In this study, we developed novel constructs for synapse-targeted chemically induced translocation (SynCIT) of specific enzymes, with the aim of inducing dendritic spine enlargement across a wide range of the brain. In dissociated cortical cultures, we confirmed the translocation of fluorescent proteins conjugated with the enzyme into spines following chemical manipulation. Consequently, we observed a sustained increase of approximately 50% in spine size over several hours. When using a non-functional mutant enzyme, spines did not enlarge despite its translocation into spines, suggesting the enlargement was enzyme activity-dependent. Furthermore, whole-cell recordings of evoked excitatory postsynaptic currents (EPSCs) in hippocampal slice cultures demonstrated functional potentiation of synapses. No significant changes were observed in activity-independent intrinsic spine fluctuation and membrane properties before and after the chemical manipulation. To validate spine enlargement in vivo, we sparsely expressed SynCIT constructs and cell fillers using a double-floxed inverted open (DIO) reading frame system combined with low Cre expression. Two-photon microscopy in the primary visual cortex confirmed sustained spine enlargement in vivo. Finally, to investigate the behavioral effects of spine enlargement in pyramidal neurons, SynCIT constructs under the CaMKII promoter were expressed brain-wide using AAV-PHPeB. Unexpectedly, chemical manipulation resulted in an increase in non-rapid eye movement (NREM) sleep. Thus, SynCIT holds promise for investigating the causal relationship between synaptic changes, which have been shown to occur in response to the physiological sleep-wake rhythm, and sleep regulation.

Disclosures: **T. Sawada:** None. **H. Okazaki:** None. **T. Arima:** None. **Y. Iino:** None. **S. Zhou:** None. **C. Shimizu:** None. **S. Yagishita:** None. **S. Shi:** None. **H. Kasai:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.09/D4

Topic: B.05. Synaptic Plasticity

Title: Connectomic analysis of sensory deprivation-induced circuit plasticity in mouse barrel columns

Authors: *K. SONG, M. SIEVERS, A. MOTTA, M. SCHMIDT, M. HELMSTAEDTER; Max-Planck Inst. For Brain Res., Frankfurt Am Main, Germany

Abstract: How experience shapes neural circuits has been extensively studied at the level of synapses, dendritic spines, dendrites, and axons. How sensory experience shapes neural circuits at the connectomic scale, however, is still elusive. 3D electron microscopy (3D-EM) connectomics is enabling the locally complete mapping of neural circuits at synaptic resolution. The development of large-scale high throughput 3D-EM methods has made it practically feasible to reconstruct neural circuits in cortical samples at about 1 mm^3 volume. Here, we studied

experience-dependent circuit plasticity in the mouse whisker-touch sensory system, in which the clear whisker-to-barrel column anatomical relationship enables the unique identification of cortical columns. Moreover, the size of the barrel columns (~300 micrometers in diameter) makes it feasible to reconstruct the entire columnal circuit by state-of-the-art analysis methods. Finally, the substantial effects of sensory deprivation induced by whisker trimming facilitate experimental operation and circuit analysis. We applied whisker trimming in a chessboard pattern in adult mice for one month, followed by the preparation of 3D-EM samples comprising at least one sensory-deprived barrel column and one neighboring non-deprived barrel column. Our sampling method achieved micro-meter precision with the use of micro-CT. Afterwards, we cut the sample into continuous ultrathin section series by ATUM, with a section thickness of 35 nm and section size of about 1.5*1.5 mm^2, for more than 10,000 sections. The sections were then imaged by a multi-beam SEM (Zeiss) with a pixel size of 4 nm, resulting in a final dataset of about 1.5 PB. We are now analyzing the circuits for connectomic consequences of adult sensory deprivation.

Disclosures: K. Song: None. **M. Sievers:** None. **A. Motta:** None. **M. Schmidt:** None. **M. Helmstaedter:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.10/D5

Topic: B.05. Synaptic Plasticity

Title: Connectomic analysis of astrocyte-synapse interactions in mouse barrel cortex

Authors: *Y. YENER, A. MOTTA, M. HELMSTAEDTER;
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Abstract: While astrocytes are well known for their metabolic support to neurons, in the last couple of decades their possible role as a synaptic partner has been considered, giving rise to the notion of “tripartite” synapses. Astrocytes express sensors for neurotransmitters released by synapses and they are thought to release chemicals associated with neuromodulation. Because of their complex morphology with a high surface-to-volume ratio, each astrocyte can contact thousands of synapses in its cellular territory. The study of the spatial nature of the contact between synapses and astrocytes requires a nano-scale resolution imaging modality. The peri-synaptic astrocytic processes, which can also get as thin as tens of nanometers, can be difficult to precisely classify automatically due to their complex morphology. Thus, a systematic mapping of the glia-connectome interaction in cortex is still lacking. Here, we developed classifiers for voxel-wise classification of astrocytes using convolutional neural networks. This enabled us to quantify the nature of the contact between synaptic elements and the peri-synaptic glial processes that partially wrap around synapses. Using a previously published 3D EM dataset from mouse cortex (Motta et al., 2019; n=200,507 synapses), we systematically analyzed the spatial relation

between astrocytes and synapses. We observed that there is a strong dependence of the fraction of astrocyte processes at the periphery of dendritic spine synapses on synapse size. Importantly, this effect is absent in other synapse types and does not occur for random non-synaptic interfaces. We furthermore found glial coverage to depend on connectomic types, such as thalamocortical axons, smooth dendrites, inhibitory synapses, and investigated its properties as a possible indicator of recent synaptic activity and synaptic plasticity. Together, our data indicate the relevance of astrocytic coverage for synapse stability, and demonstrate a surprising level of specificity for particular synaptic types.

Disclosures: **Y. Yener:** None. **A. Motta:** None. **M. Helmstaedter:** None.

Poster

PSTR068. Structural Plasticity: Neurons and Networks I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.11/D6

Topic: B.05. Synaptic Plasticity

Support: Max Planck Society
Neuronex

Title: Connectomic traces of Hebbian plasticity in mouse and human cortex

Authors: *S. LOOMBA[1], A. KHALIFA[1], A. MOTTA[1], J. GEMPT[2], H.-S. MEYER[2], M. HELMSTAEDTER[1];
[1]Max Planck Inst. For Brain Res., Frankfurt Am Main, Germany; [2]Universitätsklinikums Hamburg-Eppendorf, Hamburg, Germany

Abstract: Synaptic plasticity plays a crucial role in the organization of neuronal circuits and refinement of their connectivity during learning and development. Our current knowledge of the mechanisms that underlie synaptic plasticity is primarily based on laboratory animal models, in particular rodents. Recent advancements in the accessibility of human tissue have made it feasible to perform physiological studies on human tissue slices, enabling the investigation of synaptic plasticity in human. However, how the principles of synaptic plasticity apply to the human brain remains poorly understood. In this study, we employed 3-dimensional electron microscopy of human, non-human primate and mouse supragranular cortical samples to identify the structural effects of Hebbian plasticity in connectomic data. We quantified the rate of excitatory spines undergoing synaptic weight adaptation consistent with Hebbian learning. The human cortex shows abundance of spines with large synaptic weights, a feature absent in both the mouse and non-human primate cortex. Additionally, the synaptic weights consistent with Hebbian plasticity show stronger correlations in human cortex compared to the mouse and non-human primate cortex. These results suggest that the Hebbian plasticity may be quantitatively different in the human cortex from other species. As a key confounder, age effects have to be considered for inter-species comparison, which we are currently analyzing. Together this opens

new avenues for future exploration into the functional significance and influence of these distinct plasticity characteristics.

Disclosures: S. Loomba: None. **A. Khalifa:** None. **A. Motta:** None. **J. Gempt:** None. **H. Meyer:** None. **M. Helmstaedter:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.01/D7

Topic: B.05. Synaptic Plasticity

Support: VA Center Grant RX002999-01
VA: RX002969-01A1

Title: A Spinal Cord Intravital Imaging Study of Romidepsin Efficacy for Neuropathic Pain

Authors: *C. A. BENSON[1], A. TARAFDER[2], A. M. TAN[3];
[1]Yale Univ., West Haven, CT; [2]Yale Univ., Yale Univ., New Haven, CT; [3]Yale University/VA Connecticut Healthcare Syst., Yale University/VA Connecticut Healthcare Syst., West Haven, CT

Abstract: Neuropathic pain is a severe and often debilitating condition that affects millions of people worldwide. It is associated with spinal cord injury (SCI), traumatic brain injury, multiple sclerosis, stroke and other neurological diseases. Currently available treatments have limited or no effectiveness in providing long-term relief from neuropathic pain, and the condition remains an unmet medical need. Here we present our drug-efficacy study using romidepsin, a clinically-available PAK1-inhibitor, in a repurposed indication for neuropathic pain. PAK1 is a regulatory molecule involved in the development, maturity, and stability of dendritic spines. Dendritic spines have emerged as a key morphological correlate in the presentation of hyperexcitability disorders, including chronic pain. To corroborate and extend our prior work in this field, we have implemented a unique 4D intravital imaging approach that permits real-time imaging of structural reorganization of dendritic spines within the nociceptive system of the dorsal spinal cord. Importantly, this *in vivo* imaging platform allows us to perform longitudinal neuropathic pain studies alongside drug treatment and profile dynamic changes in the same neuron over time, concomitantly with disease progression evident by behavioral studies. To assess the efficacy of romidepsin and its ability to attenuate dendritic spine dysgenesis and restore sensory function, we performed our drug studies in animals with a spared nerve injury (SNI) model of neuropathic pain. Male and female mice were treated for the first five days post SNI with 0.25mg/kg romidepsin and monitored for two weeks. As compared with uninjured baseline, SNI animals without romidepsin displayed mechanical hypersensitivity, and increased dendritic spine density and structural volatility (e.g., a measure of turnover and movement) in excitatory nociceptive neurons in superficial dorsal horn laminae, an observation consistent with ongoing neuropathic

pain. On the other hand, treatment with romidepsin in SNI animals reduced both the magnitude of volatility and dendritic spine dysgenesis. Injured animals treated with romidepsin displayed fewer behavioral symptoms of neuropathic pain two weeks following treatment. Taken together, inhibition of PAK1 using a repurposed clinical drug, romidepsin, provides significant analgesic effect and reduces underlying morphological aspects associated with the neuropathic pain phenotype.

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Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.02/Web Only

Topic: B.05. Synaptic Plasticity

Support: Natural Sciences and Engineering Research Council of Canada

Title: Exploratory analysis of cortical thickness data in low-and high fit individuals

Authors: *Y. WANG[1], A. BORÉ[2], J. TREMBLAY[2], M. DESCOTEAUX[4], F. CHAMPOUX[3], H. THÉORET[1];
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Abstract: Studies have shown widespread changes in the human brain associated with aerobic exercise (AE) likely associated with improved cardiorespiratory fitness. Among these, exercise-related grey matter (GM) changes have been reported and appear to be associated with better cognition. The effects of AE on cortical thickness have been well described in older adults, where a positive association between cardiorespiratory fitness, GM volume and cortical thickness has been reported but the impact of sustained aerobic activity in young adults remains poorly described. Here, exploratory analysis was performed on cortical thickness data that was collected in groups of highly fit and sedentary young adults. Twenty healthy sedentary individuals (< 2 hours/week AE; mean: 0.45; BMI: 22.97) were compared to 20 active individuals (> 6 hours/week AE; mean: 11.64; BMI: 22.53) and cortical thickness was measured in 34 cortical areas with FreeSurfer. Cortical thickness values were compared between groups with independent samples t-tests and correlations between cortical thickness and VO_{2max} as well as correlations between cortical thickness and body mass index (BMI) were tested with with Pearson's R. As expected, cardiorespiratory fitness (VO_{2max}) was significantly higher in active (M = 58.98; SD = 6.52) compared to sedentary individuals (M = 43.07; SD = 7.55) whereas no difference in BMI was observed. Cortical thickness was significantly lower in numerous regions

of the left (lateral and medial orbitofrontal cortex, pars orbitalis, pars triangularis, rostral anterior cingulate cortex, superior temporal cortex, frontal pole) and right (lateral and medial orbitofrontal cortex, pars opercularis) hemispheres. Only left frontal pole ($p = 0.034$) and right lateral orbitofrontal cortex ($p = 0.034$) remained significant after FDR correction. Significant negative correlations were observed between VO_{2max} and cortical thickness in the left (frontal pole) and right hemispheres (caudal anterior cingulate and medial orbitofrontal cortex), which did not survive FDR correction. No significant correlation was found between cortical thickness and BMI. The present exploratory analysis supports previous findings suggesting neuroplastic effects of cardiorespiratory fitness that may be attenuated in young compared to older individuals. This partially supports the idea that age may be a moderating factor in the association between cardiorespiratory fitness and structural plasticity.

Disclosures: Y. Wang: None. **A. Boré:** None. **J. Tremblay:** None. **M. Descoteaux:** None. **F. Champoux:** None. **H. Théoret:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.03/D8

Topic: B.05. Synaptic Plasticity

Title: Exercise-induced Exosomes Increase Adult Hippocampal Cell Genesis

Authors: *M. CONNOLLY, A. FLIFLET, P. RAVI, D. ROSU, M. D. BOPPART, J. S. RHODES;
Univ. of Illinois Urbana-Champaign, Champaign, IL

Abstract: Exosomes are membrane-bound extracellular vesicles (<200 nm) that play a significant role in intercellular communication. They are released by active muscles during exercise and carry various effector molecules. Studies have shown that exercise can lead to a transient increase in the levels of exosomes in the bloodstream. These exosomes may contribute to the beneficial effects of exercise by facilitating communication between cells and promoting physiological adaptations in the body. However, whether exosomes are able to promote the exercise-induced changes seen in the brain like increased adult hippocampal neurogenesis is presently unknown. Therefore, the present study evaluated the effects of injection of exosomes isolated from exercising male C57BL/6J mice on hippocampal neurogenesis in male sedentary C57BL/6J mice. Exosomes were collected both from mice given access to running wheels for 4 weeks and mice that were sedentary and injected into a new group of sedentary mice. New cell genesis was evaluated by quantifying bromodeoxyuridine (BrdU)-positive cells in the granular cell layer of the hippocampus. Results showed that mice receiving exosomes from exercising mice (ExerV) had a significantly greater number of BrdU-positive cells compared to mice receiving exosomes from sedentary mice (SedV) and PBS-treated controls. Additional measures currently in progress will determine whether ExerV mice show altered new cell differentiation

by comparing proportions of BrdU-positive cells that co-label with a neuron or astrocyte marker. Preliminary results show that exosomes may be necessary and sufficient to induce adult hippocampal neurogenesis during exercise.

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

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.04/D9

Topic: B.05. Synaptic Plasticity

Support: MRC-Sackler

Title: Mapping the emergence of a subcellular balance between excitatory and inhibitory synapses along dendrites

Authors: *S. HORTON[1], J. BURRONE[2];
[2]King's Col. London, [1]King's Col. London, London, United Kingdom

Abstract: Understanding the spatial organisation of synapses is essential for comprehending how neurons integrate and compute information. The aim of this project was to map the distribution of excitatory and inhibitory (E/I) synapses along pyramidal cell dendrites in the hippocampus throughout development. Our goal was to uncover the logic of how E/I synapses are arranged and chart the emergence of a balance between the two. We used fibronectin intrabodies (FingRs), expressed in individual pyramidal neurons and delivered by in utero electroporation, to fluorescently label E/I postsynaptic compartments. Confocal microscopy of large, tiled image series was used to reconstruct the entire basal dendrites of pyramidal neurons in CA1 of the hippocampus at four developmental periods: P7, P10, P14 and P21. This enabled us to map the spatial distribution of synapses across complete dendritic branches. We used serial block face scanning EM (SBFSEM) at these same developmental periods to assess synaptic distribution with high resolution. Confocal imaging of FingRs along basal dendrites revealed that the density of excitatory synapses doubled from P7 to P21, while the density of inhibitory synapses remained consistent, suggesting differences in the timeline of E/I synapse formation. Regardless of this difference, we observed a similar balance between the excitation and inhibition already present within short stretches of dendrite at all developmental timepoints ($n=2764$ excitatory and 619 inhibitory synapses across 51 dendrites from 13 cells, $p<0.05$, Spearman's rank). SBFSEM confirmed this sub-branch balance ($n=889$ excitatory and 75 inhibitory synapses from 8 dendrites, $p<0.05$, Spearman's rank). However, throughout the entire lengths of dendritic branches, excitation and inhibition were most correlated at P7. Our results indicate that the organisation of excitation and inhibition throughout the dendritic arbours of hippocampal pyramidal neurons is non-random and established early in development.

Specifically, our results demonstrate that excitation and inhibition are proportional to one another at a sub-branch level. Basal dendrites of CA1 pyramidal neurons integrate synaptic inputs locally and our findings suggest that they are well equipped to do so in a balanced manner.

Disclosures: **S. Horton:** None. **J. Burrone:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.05/D10

Topic: B.05. Synaptic Plasticity

Title: Development of high content in vitro assays for the assessment of structural neuroplasticity

Authors: ***S. ENGEL**[1], S. LARDELL[2], R. AGRAWAL[1], A. MUNGENAST[1], M. CHYTIL[1], P. KARILA[2];
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Abstract: Alterations in neuroplasticity (decreased dendritic complexity, loss of dendritic spines, and/or impaired synaptic connection) are associated with a variety of psychiatric and neurodegenerative disorders and may contribute to their pathology. Psychoplastogens, (*i.e.*, agents that can promote neuroplasticity in the brain) hold tremendous promise for treatment of such conditions. For example, ketamine has been shown to induce neuroplasticity in vivo and is an effective treatment for depression. The measurement of a compound's ability to promote structural neuroplasticity has been challenging due to assay variability and is difficult to implement in early drug discovery due to low throughput. Here, we demonstrate our achievements identifying highly reproducible, robust, and validated high throughput assays to measure structural neuroplasticity in vitro. The assays have applications both in supporting the structure activity relationship and elucidating mechanism of action for identification and prioritization of new candidate molecules. Rat (E18) cortex cells were seeded in a 384-well format, enabling single cell analysis of neurite outgrowth (NOG) or analysis of synaptic structures. Compounds were added for 6 days in vitro (DIV) for the NOG assay and for 7 to 28 DIV for the synaptogenesis assay. Cultures were then stained with antibodies for visualization of nuclei, neuronal soma, and neurites, as well as for the pre-and post-synaptic markers synapsin 1 and PSD95 in the synaptogenesis assay. Compounds were tested in concentration response-format and morphological effects induced by compounds were quantified using high content imaging (HCA), both on the population- and single-cell level in the NOG assay. In the synaptogenesis assay, optimal conditions were identified and compounds tested in their capacity to affect the number of pre- and post-synaptic structures and the colocalization thereof.
An extensive set of tool compounds was tested in the NOG assay, and for example R-ketamine, S-ketamine, donepezil and fluoxetine were active. One of the psychedelic compounds that was inactive in the NOG assay, psilocin, was active in the synaptogenesis assay on the other hand,

indicating that the two assays in combination could be valuable tools to identify and elucidate the function of molecules with novel mechanisms.
In conclusion, we have validated a high content NOG assay with excellent reproducibility and the ability to differentiate compounds based on their efficacy and potency. Using the two assays in combination will be a powerful approach to identify compounds with differential effects and understand their mechanism of action on neuroplasticity.

Disclosures: **S. Engel:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **S. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon AB. **R. Agrawal:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **A. Mungenast:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **M. Chytil:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.06/D11

Topic: B.05. Synaptic Plasticity

Support: NIH grants HD075750 and HD098117
UVA-CAS
NSF-EXPAND fellowship

Title: Structural Evidence for Oxytocin Release in the Cerebrospinal Fluid of the Prairie Vole

Authors: *E. RAMOS[1,2], G. JIRON[3], J. J. CONNELLY[2], A. ERISIR[2];
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Abstract: Prairie voles (Microtus ochrogaster) are a highly affiliative species, making them an important translational model. Many of their postpartum and pair bonding behaviors have been presumed to be modulated via the binding of oxytocin to OXTR, which is expressed in many brain regions including nucleus accumbens and rostral cerebral cortex, regions relevant to social behavior. However, the cortical areas and much of the limbic system containing OXTR do not have OXT axonal projections, suggesting that a route other than axonal release may be responsible for OXTR binding in the central nervous system. While the majority of the released OXT reaches peripheral sites through pituitary and blood circulation, it is unlikely that OXT can cross the blood brain barrier and reach the extracellular space in the brain. Cerebrospinal fluid (CSF) circulation, on the other hand, can be an efficient means for distributing OXT via the subarachnoid space that extends along capillaries deep into the brain, and to remote sites where no or few oxytocinergic fiber projections exist. OXT has been found circulating in the CSF, however, how OXT is released into CSF is unknown. We have studied the extent of OXT fibers

that are situated to release OXT into ventricular circulation and revealed an extensive network of OXT+ neuropil that is associated with the lining of the ventricles. We used immunohistochemistry brightfield, lightsheet, and electron microscopy to examine the origins and the paths of OXT expressing neurons. Using brightfield and electron microscopy, we have revealed that OXT+ dendrites and axons of the paraventricular hypothalamic nucleus (PVN) and supraoptic nucleus cells are situated along the ventricular space. Long-distance projections of OXT axons travel close to all major ventricles and regions adjacent to those ventricles, such as the periaqueductal gray and tenia tecta, have dense fiber projections. Furthermore, OXT cells are located ectopically along the ventricular surface. In addition, electron microscopy revealed that OXT+ dendrites and axons containing dense cored vesicles penetrate the ventricular lining by penetrating in between ependymal cells and contact ventricular space directly. Our observations suggest a mechanism for direct and robust OXT release into the ventricles, providing a source of OXT that is utilized by the OXTR in cerebral cortex and the limbic system.

Disclosures: E. Ramos: None. **G. Jiron:** None. **J.J. Connelly:** None. **A. Erisir:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.07/D12

Topic: B.05. Synaptic Plasticity

Support: Cosmos Scholarship
NINDS T32 Neural Injury and Plasticity

Title: Dynamic Changes in Chloride Homeostasis Coordinates Midbrain Inhibitory Network Activity during Reward Learning

Authors: *J. WOO, D. REID, A. OSTROUMOV;
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Abstract: The mechanisms underlying how rewards are learned, and how they translate into behavior have been a subject of interest to researchers and scientists since Pavlov's classical conditioning experiments in the 1890s. Recently, Gamma Amino Butyric Acid (GABA) neurons in the Ventral Tegmental Area (VTA) have emerged as key modulators of reward learning, and potential therapeutic targets for addressing addiction, depression, and other neuropsychiatric disorders. Our previous studies have shown that exposure to acute stress or nicotine down-regulates neuron-specific anion transporter, KCC2, leading to a depolarized GABAA reversal potential in VTA GABA neurons. The depolarized GABAA reversal potential results in a decreased inhibition or even paradoxical GABAergic excitation of VTA GABA neurons. In the context of drugs of abuse and aversive stimuli, this form of synaptic plasticity has been shown to enhance the formation of reward-seeking behaviors. Yet, the impact of KCC2 downregulation on specific reward-related pathways and its contribution to naturalistic reward learning remains

unknown. Here, we used the genetic labeling of active neuronal circuits to demonstrate the depolarized GABAA reversal potential in lateral VTA GABA neurons at critical time points during reward learning. These changes impact exclusively inhibitory inputs to DA projections to the lateral portions of the nucleus accumbens, which is known to play a significant role in regulating responses to cues that predict reward. Furthermore, we show that blockade of KCC2 downregulation reduces the trajectory of cue-associative learning. Subsequently, we sought to understand how a collection of inhibitory neurons undergoing this form of synaptic plasticity can influence the lateral VTA at the network level. To this end, we implanted multi-unit tetrodes and silicon probes coupled with pharmacological and genetic approaches to examine changes in neuronal networks. Our preliminary evidence shows that KCC2-mediated plasticity drives increased coordination between VTA GABA neurons. In summary, these findings suggest that synaptic plasticity, mediated by KCC2 in specific inhibitory neuronal populations in the VTA, plays a crucial role in associative reward learning. This process involves the coordination of VTA GABA neurons that innervate lateral mesolimbic circuits.

Disclosures: **J. Woo:** None. **D. Reid:** None. **A. Ostroumov:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.08/D13

Topic: B.05. Synaptic Plasticity

Support: PAPIIT IN206521

Title: Brain plastic changes induced by wheel running and paced mating evaluated by magnetic resonance imaging and neurogenesis.

Authors: *L. MENDOZA[1], T. PEREZ-SALAZAR[1], J. A. AGUILAR[1], **R. G. PAREDES**[2]; [1]Inst. De Neurobiología, UNAM, Queretaro, Mexico; [2]LIC. EN NEUROCIENCIAS, ESCUELA NACIONAL DE ESTUDIOS SUPERIORES, U. JURIQUILLA, UNAM, Mexico

Abstract: Sexual behavior and exercise are two motivated behaviors whose study has identified behavioral, plastic, and physiological changes associated with them. Paced mating allows the female to control the rate of the sexual simulation she receives by giving her the option to escape from the male compartment. Both behaviors activate the reward system and induce the formation of new neurons. What has not been studied is what happens when subjects have the possibility of displaying these two motivated behaviors simultaneously. **Objective:** This study aims to evaluate and compare longitudinal plastic changes induced by paced mating assessed by manganese enhanced magnetic resonance imaging (MEMRI) and Bromo-deoxy-uridine (Brdu) Immunohistochemistry. **Method:** Female Wistar rats (8 subjects per group),were randomly assigned to the following groups: Control (C), Paced Mating (P), Running Wheel (RW), Open Field (OF) and Running Wheel+ Paced Mating (RP); the study was carried out for ten weeks,

five days a week exercise was performed with one session of paced mating per week. In weeks 0,1,5, and 10 MRI images were obtained. **Results:** Significant differences were observed in the distance traveled by the voluntary exercise groups, the group that performed two motivated behaviors in the same session traveled greater distance on the days they performed both behaviors ($p<0.001$). No differences were found in sexual behavior parameters in the groups that paced the sexual interaction. **Conclusion:** Preliminary results indicate that subjects who performed Running + Paced Mating in the same session can perform both behaviors without detriment to either. We are analyzing the MEMRI results to eventually correlate them with the Brdu expression.

Disclosures: L. Mendoza: None. **T. Perez-salazar:** None. **J.A. Aguilar:** None. **R.G. Paredes:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.09/Web Only

Topic: B.05. Synaptic Plasticity

Support: HRZZ-IP-2019-04-3182

Title: Characteristics of extracellular matrix in the human anterior cingulate cortex

Authors: *I. BANOVAC[1,2], M. PRKAčIN[1,2], S. TRNSKI[2], M. BOBIć-RASONJA[3,2], Z. PETANJEK[1,2], N. JOVANOV-MILOŠEVIć[3,2];
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Abstract: Alterations of the brain extracellular matrix (ECM) are crucial for determining the pathophysiological processes occurring after hypoxic brain injury. Neither diffuse nor condensed ECM, in the form of perineuronal nets (PNNs), have been sufficiently researched in the human brain, especially in the cerebral cortex. In this study we analyzed the anterior cingulate cortex (ACC) from five adult human brains using double labelling immunofluorescence. The ECM markers *Wisteria floribunda* agglutinin (WFA), neurocan (NCAN) and versican (VCAN) were combined with the neuronal nuclear antigen (NeuN). The NeuN/WFA double labelled slides were quantified using Neurolucida software. Qualitative analysis revealed that diffuse WFA^+ ECM was found in layer III and the superficial white matter. Diffuse $NCAN^+$ ECM was most pronounced in layer I but was also clearly present in the deep cortical layers (V and VI) and the superficial white matter. Diffuse $VCAN^+$ ECM was most pronounced in the superficial white matter but was also clearly present in the deep cortical layers and layer. Condensed ECM was always present around $NeuN^+$ cells, confirming that these were indeed PNNs. WFA^+ PNNs were most abundant in layer III (10.94% of all $NeuN^+$ cells were surrounded by WFA^+ PNNs), followed by layers V (5.07%) and VI (4.78%), however, they were only sporadically found in

layer II and were never present in layer I. $VCAN^+$ and $NCAN^+$ PNNs were less pronounced than WFA^+ PNNs and were present mostly in the deep cortical layers. In conclusion, both diffuse and condensed ECM in the human ACC have a specific laminar distribution. Since ECM is thought to be important in synaptic plasticity, these findings have relevant implications for the functional and laminar organization of the microcircuitry in the human brain. This is critical for understanding the underlying pathophysiology of neurodevelopmental disorders and hypoxic brain injury.

Disclosures: I. Banovac: None. **M. Prkačin:** None. **S. Trnski:** None. **M. Bobić-Rasonja:** None. **Z. Petanjek:** None. **N. Jovanov-Milošević:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.10/D14

Topic: B.05. Synaptic Plasticity

Support: RGPIN/05255-2020

Title: The Role of Astrocytes on the Activity-Dependent Plasticity of the Axon Initial Segment

Authors: *R. SANZ GÁLVEZ[1,2], Y. INGLEBERT[1,2], D. VERDIER[1,2], A. KOLTA[1,2,3]; [1]Ctr. Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA), Montréal, QC, Canada; [2]Dept. of Neurosciences, [3]Dept. of Stomatology, Fac. of Dent., Univ. de Montréal, Montréal, QC, Canada

Abstract: It is well recognized that astrocytes, considered the most abundant CNS cells, can transiently control synaptic force (for seconds or minutes) and can also modulate synaptic plasticity in the long term. However, it is unknown whether they contribute to axonal plasticity. Recent studies have shown that the biophysical and structural properties of the axon initial segment (AIS), such as its length and/or location relative to the soma, change in an activity-dependent manner, as opposed to a rigid structure as previously assumed. These forms of plasticity have been associated with changes in neuronal excitability and function as a compensatory mechanism to maintain the stability of neuronal activity. This structural remodeling of the AIS has been observed using *in vivo* sensory stimulation and deprivation models or manipulations of neurons in cell culture preparations. Here, we seek to develop and validate a method to induce this form of plasticity in *in vitro* slice preparations that enable us to better manipulate glial cells in order to investigate their role. First, we compare different methods (electrical, optogenetic or localized pharmacological manipulations) and protocols of prolonged stimulation/inhibition of layer 5 pyramidal neurons of the visual cortex in acute slices to establish which ones produce an effect on the length and location of the AIS using Ankyrin G labeling. Ankyrin G is considered as the master scaffold protein and central organizer of the AIS. We have also developed a method to automate and standardize measurements of the AIS length

and location on the basis of the Ankyrin G labeling. Our preliminary results suggest that comparable paradigms using different stimulation methods cause different and sometimes opposing effects on cell excitability, but lasting effects of excitability translate into corresponding changes in the AIS length. Preliminary data also indicate that blockade of astrocytic coupling near the recorded neuron has an effect on neuronal excitability, but the mechanisms responsible for this effect and its consequences on axonal plasticity are still under investigation. This project opens the fascinating door to explore the role of astrocytes in other different forms of non-synaptic plasticity.

Disclosures: **R. Sanz Gálvez:** None. **Y. Inglebert:** None. **D. Verdier:** None. **A. Kolta:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.11/D15

Topic: B.05. Synaptic Plasticity

Title: Large-scale, Longitudinal Neural Recordings Reveal Spatially Graded, Cell-Type Specific Plasticity Following Small-Scale Ischemic Strokes

Authors: *H. Y. RATHORE[1,2], R. YIN[3], J. ZHANG[2], Y. JIN[2], F. HE[5], B. NOBLE[2], Y. SUN[2], C. XIE[3,2,4], L. LUAN[2,4,3];
[1]Applied Physics, [2]Dept. of Electrical and Computer Engin., [3]Rice Neuroengineering Initiative, [4]Dept. of Bioengineering, Rice Univ., Houston, TX; [5]Shanghai Inst. of Optics and Fine Mechanics, Chinese Acad. of Sci., Shanghai, China

Abstract: The brain possesses a remarkable ability to undergo spontaneous self-repair in response to injury such as an ischemic stroke. This dynamic and lasting restorative process involves a diverse array of neuroplastic mechanisms that are time and location dependent. Despite extensive research, there is still a lack of definitive evidence regarding neurons changing their functional response both spatially and temporally, leading to debates about the mechanism and representation of neuroplasticity. In this study, we deployed large-scale, spatially distributed electrophysiology to chronically record neural activity from hundreds of neurons through the various phases of a small-scale ischemic stroke. To ensure monitoring of neural activity under spatially graded ischemia, we use a digital micro-mirror device (DMD) to create a precise photothrombotic micro-lesion on a single barrel column with fine location control. We stimulated the whisker corresponding to the stroked barrel and simultaneously recorded from the peri-infarct tissue and further-away tissue. We classified cells based on their electrophysiological signatures and tracked the changes in neuronal populations, firing dynamics, and within-region and cross-region connectivity for six weeks that spanned pre-stroke baseline, the recovery, and chronic phases after stroke. We find that stroke induced widespread acute inhibition, followed by cell-type specific alterations in functional responses that are highly sensitive to the distance from the infarct. Specifically, we observed that one week after the occurrence of a stroke, heightened

inhibition was only evident within a limited range of a few hundred micrometers surrounding the infarct core. Conversely, in the distant cortical tissue as well as the secondary somatosensory cortex, the populational level excitation-inhibition balance remained intact. Importantly, we detected a chronic increase in firing rate of stimulus locked excitatory neurons in the distant regions from the stroke site, indicating spatially dependent functional remapping. These changes were dynamic for the first two to three weeks post-stroke, after which they stabilized, resulting in permanently altered states compared to the pre-stroke conditions. Overall, our results highlight the complex nature of post-stroke neural reorganization and underscore the crucial role of spatiotemporal specificity in understanding neuroplasticity following ischemic stroke.

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Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.12/D16

Topic: B.05. Synaptic Plasticity

Support: CONAHCYT grants 1038794
CONAHCYT grants 252808

Title: Characterization of neural dendritic morphology and biomarkers of oxidative stress in corticolimbic areas of subjects who committed suicide.

Authors: *A. VÁZQUEZ HERNÁNDEZ[1], H. TENDILLA-BELTRAN[1], Y. C. ESCRIBANO-CADENA[1], L. ARROYO-GARCÍA[2], F. GARCIA-DOLORES[3], G. FLORES ALVAREZ[1]; [1]Neuropsychiatry laboratory, Inst. De Fisiología - BUAP, Puebla, Mexico; [2]NVS Dept., Karolinska Institutet, Stockholm, Sweden, Sweden; [3]Pathology, Inst. De Ciencias Forenses, Ciudad de México, Mexico

Abstract: Suicide is a complex public health problem of idiopathic etiology that has increased considerably in recent years and was exacerbated by the COVID-19 pandemic. This pathology affects brain structures that integrate affective state, emotional memory, impulsivity, and decision-making, such as the orbitofrontal cortex (OFC) and hippocampus (HPC). Recent studies associate the pathophysiology of suicide with alterations in the regulation of oxidative stress

(OS) and the overproduction of reactive oxygen and nitrogen species, which can compromise cellular homeostasis and may be linked to changes in neuroplasticity, including neurogenesis, apoptosis, dendritic and axonal sprouting. Dendritic spines (DS) are plastic postsynaptic structures that react to multiple factors which determine their morphology and density, therefore their shape is related to their functionality and the correct synaptic transmission. It is known that in suicidal subjects, changes in these parameters may compromise the functionality of structures associated with decision-making. Therefore, we aim to analyze the neuronal morphology and the oxidative stress biomarkers in the cerebral cortex and hippocampus of suicidal subjects.The samples were obtained under the criteria of a forensic doctor of the Institute of Forensic Sciences of Mexico City, a bioethics committee, Mexican official standards (NOM-012-SSA3-2012) and the Helsinki Declaration of 1975; known data are age, sex and cause of death; they were divided into control and suicide groups and youth and adult subgroups; and immersed in paraformaldehyde and others in Golgi-Cox staining. We focused on the determination of markers associated with OS such as 3-NT, antioxidant systems such as KEAP1/NRF2, and neurotrophic factors such as BDNF in HPC with immunohistochemistry tests; we also performed characterization of changes in neural morphology (total dendritic length, dendritic order, and arborization), DS density and DS typing in layer III and V of the COF.Our results suggest that suicide victims have modifications in the Keap1/NRF2 antioxidant system, causing changes in OS markers 3-NT, and alterations in BDNF levels, these changes may provoke alterations in neuronal morphology and impair the maintenance of functional DS that mediate synapses in cerebral regions related to suicide. Thus, these post-mortem findings seem to show biochemical and structural conditions in the COF and HPC in subjects who committed suicide compared to control subjects, which may provide a breakthrough in the pathophysiology of suicide.

Disclosures: A. Vázquez Hernández: None. **H. Tendilla-Beltran:** None. **Y.C. Escribano-Cadena:** None. **L. Arroyo-García:** None. **F. Garcia-Dolores:** None. **G. Flores Alvarez:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.13/D17

Topic: B.05. Synaptic Plasticity
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Title: Microglia-mediated gating of activity-dependent spine enlargement in the medial prefrontal cortex

Authors: *M. TAJIRI, H. OMI, T. SAWADA, S. YAGISHITA;
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Abstract: Dendritic spines undergo structural plasticity during learning in the neocortex of adult mice. However, the exact signaling pathway that leads to activity-dependent spine enlargement in the neocortex remains unclear. To investigate it in single spines of layer 5 pyramidal neurons in an acute slice preparation from the medial prefrontal cortex (mPFC) of mice, we applied a spike-timing-dependent plasticity protocol (STDP) with two-photon uncaging of glutamate. STDP stimulation resulted in spine enlargement in juvenile mice (P16-21) but not in young adult mice (P35-45). Pharmacological ablation of microglia allowed spine enlargement even in young adult mice. This result suggests that microglia suppress spine plasticity in the adult mPFC. Noradrenaline (NA) is known to regulate learning in the mPFC, and microglia express NA-sensitive Gs-coupled β2 adrenoreceptor, which activates cAMP signaling. Therefore, we asked whether NA could serve as a physiological plasticity modulator signal. We found that NA enhanced spine enlargement in a β2 but not β1 adrenoreceptor-dependent manner, the latter being mainly expressed in the pyramidal neurons. Pharmacological inhibition of microglia-specific phosphodiesterase 3, which mediates activation of the microglial β2 receptor downstream signaling, also facilitated spine enlargement in the absence of NA. In contrast, NA-dependent spine enlargement was blocked by chemogenetic inhibition of cAMP signaling specifically targeted in microglia. In further investigations of the downstream mechanism of microglia-mediated inhibition, microglia-related cytokine Tumor necrosis factor-α (TNF-α) signaling suppressed spine enlargement in the presence of NA, suggesting that microglia humorally suppresses spine enlargement at the downstream of the NA action. These results demonstrate that NA disinhibits activity-dependent spine enlargement through a microglial-cAMP pathway in young adult mice, which may play a pivotal role in learning. We thus aim at further exploring the behavioral relevance of these mechanisms and also testing whether the described mechanism could be disrupted in a disease model.

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

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.14/D18

Topic: B.05. Synaptic Plasticity

Support: Ontario Graduate Scholarship
SickKids Restracomp PhD Scholarship

Title: Role of AMPA glutamate receptors in hippocampal synaptic regulation and neuronal activation during learning and memory

Authors: *R. GUGUSTEA, Y. CHEN, C. ZHAO, Z. JIA;
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Abstract: Memory is physically represented within specialized structures between neurons known as synapses. Membrane-bound receptors on synapses allow for signal transduction, of which alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) serve as the principal mediators for excitatory neurotransmission. AMPARs in the hippocampus are hetero-tetramers predominantly composed of subunits GluA1 and GluA2, which feature functionally distinct C-terminal domains (CTDs). Learning induces neuronal activation within the brain, but a mechanistic link between AMPARs and learning-induced cell activation remains unknown. This study used male and female adult age-matched wildtype (WT) and transgenic mice ($GluA1^{C2KI}$ and $GluA2^{C1KI}$ mice) featuring genetically swapped AMPAR subunit GluA1 and GluA2 CTDs and impaired synaptic function to reveal an underlying link between synaptic transmission and learning-induced cell activation. It was hypothesized that AMPARs are altered in learning-induced active cells and that the genetic modification of AMPARs to impair synaptic function will impair the activation of neuronal assemblies following learning. Mice injected with an activity-dependent viral marker into the dorsal CA1 and dentate gyrus subregions of the hippocampus underwent contextual fear conditioning (CFC) to form a long-term context-dependent memory. $GluA2^{C1KI}$ mice were impaired in long-term contextual fear memory (n = 17; $P < 0.0001$) compared to WT mice and featured reduced activity-dependent phosphorylation of the serine-831 (S831) residue on the GluA1 CTD following contextual fear conditioning (n = 6; $P = 0.0026$). Total hippocampal GluA2 protein expression was unchanged between WT, $GluA1^{C2KI}$, and $GluA2^{C1KI}$ mice including between fear-conditioned and unconditioned mice. These AMPAR-mediated impairments were associated with unchanged learning-induced cell counts in fear-conditioned versus unconditioned $GluA2^{C1KI}$ mice in the dorsal CA1 (n = 10) and dentate gyrus (n = 6) subregions, whereas both WT (n = 9; $P = 0.0432$) and $GluA1^{C2KI}$ mice (n = 10; $P = 0.0485$) featured a significant increase in cell activation following CFC. These findings suggest a critical role for AMPAR protein- and phosphorylation-related changes in neuronal activation and memory. Our results may also contribute to the understanding and treatment of brain disorders such as Alzheimer's disease, autism spectrum disorder, and intellectual disability, as dysregulation of AMPARs and synaptic function are frequently associated with these disorders.

Disclosures: **R. Gugustea:** None. **Y. Chen:** None. **C. Zhao:** None. **Z. Jia:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.15/D19

Topic: B.05. Synaptic Plasticity

Support: P01NS057228

Title: Reciprocal excitatory spinal circuits in rats with normal and reinnervated muscle

Authors: T. ROTTERMAN[1], A. S. DEARDORFF[2], ***P. NARDELLI**[1], T. COPE[1];
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Abstract: Abnormal co-contraction of limb antagonist muscles during locomotion persists following peripheral nerve transection despite successful muscle reinnervation. In attempt to explain this dysfunction, we hypothesized a change in spinal reflex circuits between muscle antagonists. Consistent with that hypothesis, we found reflex excitation in extensor gastrocnemii muscles induced by stretching reinnervated flexor tibialis anterior (TA) muscle in acutely decerebrated Wistar rats. Investigation of underlying spinal circuits in isofluorane-anesthetized rats revealed that stretching a reinnervated TA muscle evoked predominantly excitatory postsynaptic potentials (EPSPs) at di- and tri-synaptic latencies in MG motoneurons. While an alluring explanation for antagonist co-contraction after muscle reinnervation, the same result was obtained in untreated rats. Although never studied in adult rats, stretch-evoked EPSPs with polysynaptic delay were recorded in virtually all antagonist motoneurons sampled, whether from TA-->G or G-->TA. From these findings we propose a novel feed-forward excitation in a propriosensory spinal circuit that we tentatively name reciprocal excitation for its mirror image resemblance of reciprocal inhibition between antagonist muscles. Further study is required to examine, for example, the circuit's interlimb distribution and species dependence in untreated animals. Under conditions of nerve injury and regeneration, failure to find modification of reciprocal excitation turns our attention to possible alteration of spinal or descending regulation of reciprocal excitation in the awake behaving animals that exhibit abnormal co-contraction.

Disclosures: T. Rotterman: None. **A.S. Deardorff:** None. **P. Nardelli:** None. **T. Cope:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

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Program #/Poster #: PSTR069.16/D20

Topic: B.05. Synaptic Plasticity

Support: PAPIIT IN206521

Title: Identification in male rats by MEMRI, of the neural circuits controlling sexual behavior and sexual motivation with different levels of sexual experience

Authors: *L. GAYTAN[1,2], R. G. PAREDES[2], S. ALCAUTER[3], J. ORTIZ[4], J. A. AGUILAR[3];
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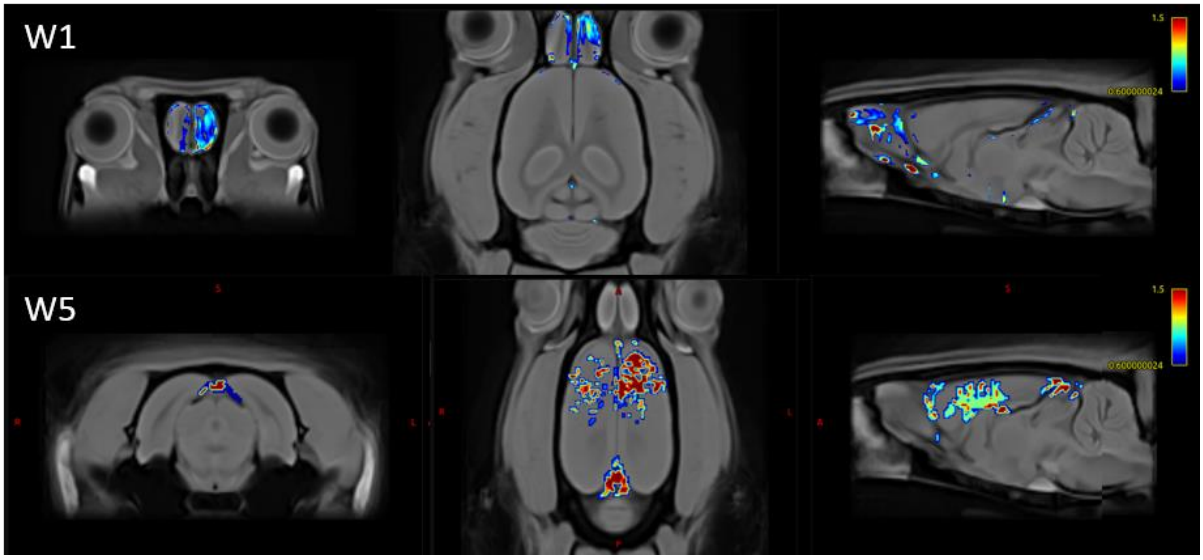
Abstract: The brain regions controlling sexual motivation and sexual behavior have been identified by different techniques, however, the influence of sexual experience on the activation of these brain regions in the same subject is unknown. Using manganese-enhanced magnetic resonance imaging (MEMRI) we analyzed the activation of brain regions in the sexual incentive motivation (SIM) and the partner preference tests (PP), on weeks 1, 5 and 10, in male rats tested for 10 weeks. AIMS. In experiment 1 we analyzed the possible toxic effects of a dose of 16 mg/kg of $MnCl_2$ on male sexual behavior, wheel running, and motor execution. In experiment 2 subjects were tested for sexual incentive motivation (SIM) or partner preference (PP) using magnetic resonance. METHODS. In both experiments, a dose of 16mg/kg (s.c) of chloride manganese ($MnCl_2$) was administered 24 h before subjects were tested and placed immediately thereafter in a 7 tesla Brucker scanner. RESULTS. In experiment 1 the dose of 16mg/kg of MnCl2 did not induce behavioral alterations that could interfere with the interpretation of the imaging data. In experiment 2, we found a higher signal intensity in the OB in week 1 in SIM vs the control group. We also found an increase in signal intensity in the socio-sexual and reward circuits in the SIM test, in week 1. In the PPT task we found a higher signal intensity in the VTA in week 10 vs control group. We also observed an increase in signal intensity in PP group in week 5 vs the control group in the socio-sexual and reward circuits. The Cohen's D analysis for the activity of the whole brain in the SIM group, revealed that as the subjects gain sexual experience a higher activation of the OB is observed. In the PPT group as the subjects gain sexual experience the higher the activation in the frontal cortex and subcortical structures. CONCLUSION. As the subjects acquire sexual experience a higher brain activation is observed as more structures belonging to both the reward and the socio-sexual circuits are recruited.



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Poster

PSTR069. Structural Plasticity: Neurons and Networks II

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Topic: B.05. Synaptic Plasticity

Support: Tis research was supported by Shota Rustaveli National Science Foundation of Georgia under award number FR-21-1501 and Ivane Beritashvili Center of Experimental Biomedicine.

Title: Chronic white noise effects of the rat hippocampus's ultrastructure

Authors: *N. POCHKHIDZE[1], M. ZHVANIA[2], N. JAPARIDZE[3], G. LOBZHANIDZE[3]; [1]Cell. Neuroscience; Lab. of Brain of Ultrastruchture and Nanoarchitechtonics, Ilia State University, I. Beritashvili center of Exptl. Biomedicine, Tbilisi, Georgia; [2]Cell. Neuroscience; Lab. of Brain of Ultrastruchture and Nanoarchitechtonics, Ilia State University; Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [3]Lab. of Brain of Ultrastruchture and Nanoarchitechtonics, Ivane Beritashvili center of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: Objectives/Introduction: Noise pollution is a significant problem for public health. High intensity white noise (HIWN) affects many systems of the organism, including central nervous system. Specifically, HIWN provokes various neurological and/or neuropsychiatric symptoms, including sleep disorders, altered cognition, and emotions. Methods: In the present study, using transmission electron microscopy (TEM), we assessed the ultrastructural alterations in the hippocampus CA1 area of the rat following HIWN. Rats were exposed to 100 dB of noise for one hour daily for 30 consecutive days. The evaluation was performed on Day 31. Besides qualitative description, quantitative analysis of some parameters of axon-dendritic and axon-spine synapses was performed. One-way ANOVA and two-sample t-test of quantitative data were used. Results: Mainly moderate alterations were found, but in some cases, irreversible modifications, such as neuronal apoptosis, chromatolysis and significant destructions of several cytoplasm organelles were described. In addition, in some places, significant glial activation was present. Some quantitative changes were also present. The most significant were alterations in presynaptic mitochondria and the number of synaptic vesicles. Specifically, the decrease of the total number of vesicles was detected. Such results suggest that due to continuous transmission, the majority of vesicles are unable to replenish their cargo via transporters. Conclusion: The results provide evidence that detrimental effects of loud noise are reflected on the hippocampus ultrastructural level. Tis research was supported by Shota Rustaveli National Science Foundation of Georgia under award number FR-21-1501 and Ivane Beritashvili Center of Experimental Biomedicine.

Disclosures: N. Pochkhidze: None. **M. Zhvania:** None. **N. Japaridze:** None. **G. Lobzhanidze:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.18/D22

Topic: B.05. Synaptic Plasticity

Support: The Netherlands Research Council NWO Vici 865.17.003 (MK)
The Netherlands Research Council NWO Veni.192.242 (AF)

Title: Sodium channel endocytosis drives axon initial segment plasticity

Authors: *A. FREAL[1], N. JAMANN[2], N. PETERSEN[3], C. C. HOOGENRAAD[4], M. H. KOLE[3];
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Abstract: The axon initial segment (AIS) is a critical domain of all excitable neurons which maintains neuronal polarity and functionally acts as the final synaptic integration site for action potential generation. Activity-dependent plasticity of the AIS endows neurons with the ability to adapt action potential output to changes in network activity. Action potential initiation at the AIS highly depends on the isoforms, distribution and density of voltage-gated sodium channels (Na_V), but the molecular mechanisms regulating their plasticity remain largely unknown. Here, we developed genetic tools to label endogenous Na_V channels and their scaffolding protein AnkyrinG. This labeling strategy allowed us to reveal their nanoscale organization and longitudinally image AIS plasticity in hippocampal neurons in slices and primary cultures. We find that NMDA receptor activation causes both long-term synaptic depression and rapid AIS structural remodeling. During this rapid plasticity, AnkyrinG length is reduced and the distal pool of $Na_V1.2$ channels is lost. We further show that AIS shortening requires clathrin-mediated endocytosis and we observe an increased density of endocytic structures specifically at the distal AIS during plasticity, which colocalize with intracellular $Na_V1.2$ channels. Moreover, experiments combining live imaging of AnkyrinG during electrophysiological recordings show that reduced AIS length correlates with increased threshold for action potential generation. Thus, rapid AIS plasticity is driven by the internalization of distal $Na_V1.2$ channels and tunes neuronal output. These data reveal a fundamental mechanism for rapid activity-dependent AIS reorganization and suggests that plasticity of intrinsic excitability shares conserved features with synaptic plasticity.

Disclosures: A. Freal: None. **N. Jamann:** None. **N. Petersen:** None. **C.C. Hoogenraad:** A. Employment/Salary (full or part-time):; Genentech, Inc. **M.H. Kole:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.19

Topic: B.05. Synaptic Plasticity

Support: CONVOCATORIA PARA LA FINANCIACIÓN DE PROYECTOS DE SEMILLEROS DE INVESTIGACIÓN EN LA FACULTAD DE MEDICINA DE LA UNIVERSIDAD NACIONAL DE COLOMBIA 2020. Hermes Código: 50305

Title: In rats, the maternal separation during breastfeeding induces an increase in the number of astrocytes in cerebellum, and the enriched environment reduces this effect.

Authors: J. MORA-PLATA, M. JÁCOME-SANDOVAL, J. CEBALLOS-ORDOÑEZ, *Z. DUENAS;
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Abstract: Stress is a biological response that occurs when an organism perceives and/or suffers a disturbing or harmful event that has consequences in its homeostasis. In early stages of life, it can manifest in various forms such as neglect, abuse, physical or emotional abandonment, among others. Animal models are widely used to study the consequences of early stress on the brain; thanks to them, it is known that Maternal Separation during Breastfeeding (MSDB) is a chronic stressor and induces both morphological and physiological changes that can even manifest themselves at the behavioral level. In this topic, however, the cerebellum, which in the central nervous system performs a regulatory role, not only in motor activity but also in cognitive and affective behaviors, has been studied to a lesser extent. Using this model, the aim of the study was to determine whether MSDB and subsequent exposure to an Enriched Environment (EE) affected the number of astrocytes in the Ansiform lobule (AL), Paraflocculus (PF), and Deep Cerebellar Nuclei (DCN). Separated and unseparated male and female Wistar rats, with and without an enriched environment, were used for this study. Cerebellum sections from 57 Wistar rats, divided according to sex and exposure to MSDB and EE, were processed by immunohistochemistry for glial fibrillary acidic protein (GFAP). Manual counting of labeled astrocytes was performed using the ImageJ software in the areas studied, and significance analysis was carried out initially by means of Student's T-test. The results show that MSDB induces a significant increase in the number of astrocytes in the cerebellum in both females and males. Similarly, EE also produces an increase, although in smaller proportion, and EE after MSDB reduces the number of labeled astrocytes almost equal to the effect of AE in females, but not in males, where the number of labeled cells remains higher compared to controls. These results suggest that maternal separation increases glial activity in the cerebellum, apparently as a consequence of the neural damage generated by the stress model, and that EE possibly achieves an attenuation of that hyper-reactivity, emerging as a neuroprotective agent. However, as a single factor, EE could also be related to stress generation in these areas.

Disclosures: J. Mora-Plata: None. **M. Jácome-Sandoval:** None. **J. Ceballos-Ordoñez:** None. **Z. Duenas:** None.

Poster

PSTR069. Structural Plasticity: Neurons and Networks II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.20/D23

Topic: B.05. Synaptic Plasticity

Support: RO1 Grant AG061787
RO1 Grant MH099114
The Hartwell Foundation

Title: Notch system facilitates extracellular vesicle-based neuronal communication

Authors: *K. GEBIS[1], Y.-Z. WANG[1], J. N. SAVAS[1], A. CONTRACTOR[2], C. C. M. CASTILLON[2], E. T. BARTOM[3], A. D'AZZO[4];
[1]Neurol., [2]Neurosci., [3]Biochem. and Mol. Genet., Feinberg Sch. of Med., Chicago, IL; [4]Genet., St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Extracellular vesicles (EVs) facilitate intercellular communication by transferring cargo between cells in a variety of tissues. However, how EVs achieve cell type-specific intercellular communication is still largely unknown. We found that Notch1 and Notch2 proteins are expressed on the surface of neuronal EVs that have been generated in response to neuronal excitatory synaptic activity. Notch ligands bind these EVs on the neuronal plasma membrane, trigger their internalization, activate the Notch signaling pathway, and drive the expression of Notch target genes. The generation of these neuronal EVs requires the ESCRT-associated protein Alix. Adult Alix conditional knockout mice have reduced hippocampal Notch signaling activation and glutamatergic synaptic protein expression. Thus, EVs facilitate neuron to neuron communication via the Notch receptor-ligand system in the brain.

Disclosures: K. Gebis: None. **Y. Wang:** None. **J.N. Savas:** None. **A. Contractor:** None. **C.C.M. Castillon:** None. **E.T. Bartom:** None. **A. d'Azzo:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.01/Web Only

Topic: B.09. Glial Mechanisms

Support: CIHR Grant PGT165852
CIHR Postdoctoral Fellowship 202110MFE-472592-FPP-CEAH-93191

Title: Astroglial and neuronal calcium dynamics in response to acute and chronic stress in mice

Authors: *Y. BANSAL[1], S. CODELUPPI[1], J. MUIR[2], R. C. BAGOT[2], E. SIBILLE[3], M. BANASR[4];
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Toronto, Toronto, ON, Canada; [4]Neurobio. of Depression and Aging, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Astrocytes are ubiquitous glial cells in central nervous system that regulate synaptic transmission and neurotransmitter recycling through bidirectional interaction with neurons. Specifically, astrocytes respond to altered neuronal activity through changes in intracellular Ca^{2+} concentrations and release gliotransmitters, which in turn act on neurons. Emerging research identify a critical role of astroglial dysfunctions in the major depressive disorder- and stress-related synaptic deficits. Thus, investigating changes in astroglial and concomitant neuronal Ca^{2+} transients in response to stress may help elucidate the astroglial involvement in depressive-like symptoms. In this study, neuronal and astroglial Ca^{2+} transients were recorded using fiberphotometry in freely moving mice. Astroglial and neuronal specific adeno-associated viruses were infused in the prefrontal cortex to record Ca^{2+} transients using fiber optic cannula. We first investigated the changes in astroglial and neuronal Ca^{2+} mobilization baseline activity and reactivity to acute stress (tail pinch and immobilization stress). In addition we also examined concurrent neuronal and astroglial Ca^{2+} transient alterations longitudinally in response to acute stress (immobilization stress once per week) and chronic stress (unpredictable chronic mild stress) for 5 weeks. This work allowed us to identify the cell activity alterations in response to acute and chronic stress and shed light on the dynamic relationship between the astrocytic and/or neuronal dysfunctions associated with stress.

Disclosures: Y. Bansal: None. **S. Codeluppi:** None. **J. Muir:** None. **R.C. Bagot:** None. **E. Sibille:** None. **M. Banasr:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.02/D24

Topic: B.09. Glial Mechanisms

Support: PR-LSAMP
NARSAD Young Investigator Award from Brain & Behavior Research Foundation

Title: Astrocytic and neuronal lactate metabolism in the brain of Angelman Syndrome mice

Authors: *A. VARGAS VIRELLA, K. GARCÍA CORTÉS, Z. MARTÍNEZ FIGUEROA, E. CRUZ;
Biomed. Sci., Pontifical Catholic Univ. of Puerto Rico, Ponce, PR

Abstract: Angelman Syndrome (AS) is a neurodevelopmental disorder characterized by severe cognitive disability, impaired motor coordination, and epilepsy. The cause is related to a loss of expression of the maternally expressed and paternally imprinted UBE3A gene. No specific treatment is currently available for AS, however, recent studies identified brain metabolism as a

new method of treatment. In this study, we hypothesized that a dysregulation of UBE3A leads to astrocytic and neuronal lactate metabolic impairments. To address this hypothesis, we measured the levels of the astrocytic marker (GFAP), neuronal marker (β3-Tubulin), monocarboxylate lactate transporters (MCT2 and MCT4), and lactate dehydrogenases (LDHA and LDHB) in the hippocampus of a mouse model carrying the UBE3A mutation and exhibiting the symptoms associated with AS. Given the strong association of cognitive deficits with the hippocampus, our study focused on this brain structure. The hippocampus mediates memory consolidation, the process by which new information is stabilized, resulting in the storage of enduring memories. We also tested whether hippocampal 100 nmol L-lactate administration can rescue cognitive impairments in UBE3A mice. Interestingly, we found that GFAP and β3-Tubulin levels were significantly higher in the hippocampus of AS mice. This suggests a higher abundance of astrocytes and neurons; therefore, these cells may lack the necessary metabolic tools, which could lead to the memory impairments associated with the disorder. Further studies are required to examine whether modulation of these markers can rescue the memory deficits found in AS mice.

Disclosures: A. Vargas Virella: None. **K. García Cortés:** None. **Z. Martínez Figueroa:** None. **E. Cruz:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.03/D25

Topic: B.09. Glial Mechanisms

Support: Swedish research council 2018-02814
Swedish research council 2020-00559

Title: Impaired astrocyte function may underly nicotine-induced synaptic depression in the dorsal striatum of Wistar rats

Authors: *L. ADERMARK, E. LUCENTE, O. LAGSTRÖM, K. ADEMAR, B. SÖDERPALM, M. ERICSON;
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Abstract: The psychoactive component of tobacco, nicotine, modulates neurotransmission in multiple brain regions including the dorsolateral striatum (DLS), a brain region associated with the formation of habits. The microcircuits and signaling pathways engaged by nicotine are however not fully understood. The aim of this study was to outline the role of astrocytes in mediating the acute effects by nicotine on striatal neurotransmission. To this end, we performed *ex vivo* electrophysiological recordings and *in vivo* microdialysis combined with metabolic, chemogenetic, and pharmacological manipulations in Wistar rats. *Ex vivo* electrophysiological recordings demonstrated that nicotine (1 μM) suppressed synaptic output by reducing the

frequency of excitatory inputs onto medium spiny neurons (MSNs). Inhibition of astrocytes using either the metabolic inhibitor fluorocitrate, GFAP-targeting DREADDs, or the glial-specific glutamate transporter inhibitor TFB-TBOA also reduced striatal output, and occluded nicotine-induced synaptic depression. Nicotine-pretreatment further occluded synaptic depression induced by inhibition of astrocytes. Synaptic depression induced by either nicotine or astrocytic inhibition was blocked in slices pre-treated with an mGluR5 antagonist, suggesting that elevated levels of extrasynaptic glutamate could underly synaptic depression. To further establish a putative inhibition of astrocytes by nicotine, changes in extracellular amino acid levels were assessed by *in vivo* microdialysis during systemic administration of nicotine (0.36 mg/kg free base). Nicotine significantly increased the microdialysate level of glutamate, but decreased the extracellular concentration of glutamine, indicative of an impaired astrocytic glutamate-glutamine shuttle following nicotine exposure. We suggest that nicotine-induced synaptic depression involves a plastic interplay between astrocytes and neurons, and that mGluR5 receptors are involved in nicotine induced effects on striatal neurotransmission.

Disclosures: L. Adermark: None. **E. Lucente:** None. **O. Lagström:** None. **K. Ademar:** None. **B. Söderpalm:** None. **M. Ericson:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.04/D26

Topic: B.09. Glial Mechanisms

Support: Ann Hanley Neuroscience Fund (University of Kentucky)
NEU STAR, Department of Neurosurgery (University of Kentucky)
BRAIN Alliance

Title: Injury-induced glial and nonglial cell activation in human peripheral nerve tissues

Authors: *P. V. MONJE[1], J. E. QUINTERO[1], G. I. APARICIO[1], M. J. CHAU[1], A. S. WELLEFORD[2], G. A. GERHARDT[1], C. G. VAN HORNE[1];
[1]Dept. of Neurosurg., [2]Dept. of Neurol., Univ. of Kentucky, Lexington, KY

Abstract: Our understanding of nerve injury mechanisms is based, almost entirely, on rodent models of nerve damage. To examine injury-induced changes in nerve cells from humans, we compared donor-matched intact and transected nerve tissues (sural nerve) from subjects undergoing experimental axotomy as part of a nerve transplantation clinical trial (NCT02369003). Our study compared high resolution transcriptomics [bulk and single nuclei (sn) RNAseq], proteomics analysis, and immuno-histological observations of fixed tissue samples. Our results provided evidence of myelin phagocytosis by human Schwann cells (SCs), downregulation of myelinating SC-associated genes, and increased NGFR protein expression, a marker of repair (injury-activated) SCs, two weeks after injury. However, transcriptional

reprogramming, cell cycle re-entry, and increased expression of typical SC markers (SOX10, S100B) were not evident in the SC groups. Surprisingly, the injury promoted dramatic changes, including proliferation, in cells from the connective tissue layers and the vasculature. Immunostaining analysis evidenced the existence of distinct injury-responsive NGFR positive, S100B negative, SOX10 negative, nonglial cells located within the perineurium and the epineurium, and surrounding the blood vessels. Similar to SCs, these nonglial cells reacted to the injury by strongly upregulating NGFR in their respective compartments. Accordingly, snRNAseq revealed three major heterogeneous groups of cells which fully reprogrammed their transcriptome after injury. These heterogeneous cells, which clustered independently of the SC groups, contained assorted mesenchymal stem cell genes (e.g., PDGFRA, EGFR, PRRX1, and TWIST1/2) and jointly increased epithelial-to-mesenchymal transition and extracellular matrix remodeling signaling after injury. Most importantly, our combined proteomics, transcriptomics, and immunochemical analysis confirmed that the above-mentioned responses were consistent among various donors. In summary, our studies evidenced an unexpected contribution of nonglial, mesenchyme-like cells to the SC-mediated injury response in human nerves.

Disclosures: P.V. Monje: None. **J.E. Quintero:** None. **G.I. Aparicio:** None. **M.J. Chau:** None. **A.S. Welleford:** None. **G.A. Gerhardt:** None. **C.G. van Horne:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.05/D27

Topic: B.09. Glial Mechanisms

Support: The New York Empire Innovation Program Grant to SGW
SUNY Optometry Start-up Funds to SGW
Graduate Assistantship to DL
T-35 Award to AR

Title: The impact of microRNA loss in Muller glia cells on retinal degeneration and gliosis

Authors: D. LARBI, M. D. ANDRADE, S. CHEN, A. RIEF, S. VISWANATHAN, *S. G. WOHL;
Biol. and Vision Sci., State Univ. of New York, Col. of Optometry, New York, NY

Abstract: In the neural retina, Müller glia (MG) reactivity (gliosis) leads to exacerbation of neuronal loss and rapid deterioration of vision. Finding key regulators of gliosis is important to developing approaches to prevent blindness. Potential key regulators appear to be microRNAs (miRNAs), negative regulators of gene expression. MG have a unique set of miRNAs that have been shown to be crucial for their proper function. Whether MG miRNAs regulate gliosis is however still unclear. A model for retinal degeneration as it occurs in retinitis pigmentosa for example, is light damage. We established a moderate model by exposing mice to 5,000 lux of

diffuse, cool, white light for 4 hours. To investigate the MG response, we utilized MG-specific reporter mice (*RlbpCreER: stop$^{f/f}$-tdTomato*, wildtype). miRNAs were depleted in MG by crossing the MG reporter mice with Dicer knockout mice (cKO). To evaluate retinal structure and function, *in vivo* retinal imaging with optical coherence tomography (OCT) and electroretinogram (ERG) recordings were performed. Immunofluorescent labeling and confocal microscopy were used to assess the histology of the retina and cellular features. The evaluation of the degree of neuronal degeneration showed that retinas of light-damaged cKO mice displayed less retinal thinning and less impaired ERGs than light-damaged wildtype retinas. In particular, the scotopic b-wave response was significantly lower in damaged wildtype mice compared to damaged cKO mice suggesting preservation of inner retinal function. Evaluation of Calbindin and Choline Acetyltransferase labeling, both markers for retinal interneurons, showed less disruption of neuronal processes in damaged cKO retinas, confirming our ERG data. Furthermore, MG of damaged wildtype retinas showed features of both unspecific and specific gliosis, i.e., upregulation of GFAP and downregulation of glutamine synthetase (GS) respectively. MG of cKO mice however displayed reduced reactive glia response, i.e., less glial fibrillary acidic protein (GFAP) expression and a rather stable GS expression, suggesting that the loss of miRNAs leads to diminished gliosis. Underlying pathways appear to include the STAT pathway and miR-125b. Taken together, these results support the hypothesis that MG-miRNAs play a role in the regulation of MG gliosis. This gives hope to the use of MG miRNAs as a potential therapeutic tool to attenuate gliosis and preserve retinal integrity and function in retinal disease.

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Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.06/D28

Topic: B.09. Glial Mechanisms

Support: FAPESP # 2022/14077-4
FAPESP # 2018/05006-0

Title: Impact of TNF-alpha deactivation on motoneuron survival, glial reaction and functional recovery after spinal cord root avulsion and reimplantation

Authors: *J. S. FRARE[1], L. P. CARTAROZZI[1], R. S. FERREIRA JR.[2], B. BARRAVIERA[2], A. L. OLIVEIRA[1];
[1]Mollecular and Morphofunctional Biol., Univ. of Campinas - Lab. of Nerve Regeneration, Campinas, Brazil; [2]Ctr. for the Study of Venoms and Venomous Animals (CEVAP), São Paulo State Univ., Botucatu, Brazil

Abstract: Tumor necrosis factor-alpha (TNF-α) is a key cytokine that is directly linked to inflammation and decreased regenerative capacity following spinal cord injury. Exacerbated local inflammation, mediated by astrogliosis and reactive microglia, contributes to further motoneuron loss after spinal ventral root avulsion (VRA). Thus, we evaluated the neuroprotective and immunomodulatory capacity of Etanercept (ET), a drug that consists of a soluble TNF-α receptor (a dimeric fusion protein of the p75 receptor and the Fc portion of human IgG) that binds to circulating TNF-α. Firstly, we established a dose-response curve using different concentrations and administration schemes following VRA. For that, 35 female C57BL/6 mice (N=5/group) underwent VRA and reimplantation using a fibrin sealant. They were divided into five groups, such that the first four groups received ET intraperitoneally one hour after the injury, and on the third, sixth, and ninth days thereafter as follows: VRA + reimplantation + vehicle (VE); VRA + reimplantation + 3 mg/kg ET (ET3); VRA + reimplantation + 6 mg/kg ET (ET6); VRA + reimplantation + 9 mg/kg ET (ET9). The last group received ET only from the third day post-injury: VRA + reimplantation + 6 mg/kg ET – late treatment (ET6L). All experiments were approved by the Institutional Committee for Ethics in Animal Use (CEUA/IB/UNICAMP; Brazil, protocol number 6161-1/2022). Four weeks postoperatively, animals from all groups were euthanized, and spinal cords were prepared for motoneuron counting (Nissl staining) and immunohistochemical evaluation of astroglial and microglial reactions (anti-GFAP and anti-Iba-1, respectively). Also, during 12 weeks, the sciatic functional index (SFI), regularity index, and base of support for the hind limbs were assessed using the walking track test (CatWalk System, Noldus) in the long-term VE and ET6 groups (N=5/group). The results showed a significant improvement in neuronal survival in the ET6 group ($p=0.007$), combined with reduced astrogliosis, which was also decreased in the ET6 ($p=0.017$) and ET9 ($p=0.019$) groups, compared to the vehicle counterpart. However, none of the ET therapies, including ET6, showed long-term functional improvements ($p>0.05$) based on a 12-week evaluation. We hypothesized that inhibition of TNF-α, although neuroprotective, impaired axonal regrowth of motor axons towards the reimplanted spinal roots. These findings suggest that deactivating TNF-α in the acute and subacute phases after ventral root avulsion may have to be combined with additional strategies to stimulate axonal growth, such as the use of neurotrophic factors.

Disclosures: **J.S. Frare:** None. **L.P. Cartarozzi:** None. **R.S. Ferreira Jr.:** None. **B. Barraviera:** None. **A.L. Oliveira:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.07/D29

Topic: B.09. Glial Mechanisms

Support: Lundbeckfonden 313-2019-606
IRFD 8020-00118A

Title: Visualization and Profiling of mouse Schwann Cell-Derived Exosomes in vivo

Authors: *C. VAEGTER[1], R. ROSSI[1], M. RICHNER[1], N. GONCALVES[1], O. AHLGREEN[1], Y. YANG[2], L. T. PALLESEN[1];
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Abstract: Exosomes are nanoscale extracellular vesicles involved in intercellular communication. Previous studies exploring the role of exosomes in neurobiology have primarily been conducted using exosomes derived from cell culture systems, providing foundational knowledge of their biochemical composition and potential functions. However, these *in vitro* models may not fully recapitulate the intricate, dynamic environment in which Schwann cells (SCs), the principal glia of the peripheral nervous system (PNS), release exosomes and interact with neurons. SC-derived exosomes are assumed to be implicated in nerve development, regeneration, and pathogenesis through their complex cargo of bioactive molecules. Yet, a comprehensive characterization of their distribution and impact on peripheral axons *in vivo* remain elusive.To bridge this gap, our study employs fluorescently tagged SC-derived exosomes to visualize and analyze these entities within a live animal model. The first objective is to establish a mouse model for visualizing these tagged exosomes using electron microscopy (EM), examining their *in vivo* distribution under physiological conditions as well as after nerve crush injury. This approach aims to provide an unprecedented, dynamic picture of SC-derived exosome behavior and interaction in a realistic, physiological context. Our second objective is to isolate tagged SC-derived exosomes from peripheral nerve tissue for downstream RNA-Seq and bioinformatics analysis, allowing us to hypothesize about their potential roles in neural communication and pathogenesis.The study aims to bring new insights into the role of SC-derived exosomes in the PNS, paving the way for an enhanced understanding of their contributions to neurological processes.

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Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.08/D30

Topic: B.09. Glial Mechanisms

Title: Glia-derived adenosine in the vHPC is involved in trigeminal neuralgia-induced anxiodepression

Authors: *X. LYU, S. LYU, G. WANG, Y. ZHANG;
Fudan Univ., Shanghai, China

Abstract: Chronic pain often co-occurs with mood disorders such as anxiety and depression. The ventral hippocamps serve as a critical limbic cortical region in chronic pain and emotion. But it is unknown whether and how ventral hippocampus gliocyte involves chronic pain-induced anxiodepression. Here, we found that astrocytes and microglia in the ventral hippocampus synergistically mediate the up-regulation of adenosine content in the chronic pain model unilateral chronic constriction injury of infraorbital nerve (CION), and adenosine acts on adenosine A2A receptors in $CaMK2A^+$ neurons in CA1 to increase neuronal excitability and mediate the anxiodepression-like behaviors. Specifically, microdialysis showed that adenosine levels in the ventral hippocampus increased 14 days after CION, and using pharmacological approaches inhibiting the connexin 43 (Cx43) or ectonucleotidases (CD39) reversed these alterations and had anxiolytic and anti-depressant effects. The same result may be obtained by respectively pharmacological or optogenetic inhibiting active astrocytes and microglia in the ventral hippocampus. Knockdown adenosine A2A receptor on CA1 $CaMK2A^+$ neurons prevent CION-induced anxiodepression-like behavior. Furthermore, we showed that adenosine induced anxiety-like behavior by increasing the excitability of $CaMK2A^+$ neurons. These findings imply that ventral hippocampus glial cells are implicated in the co-morbid anxiety and depression of chronic pain, and that the control of adenosine content and its A2A receptor may be a potential therapeutic target for the co-morbid anxiety and depression of chronic pain.

Disclosures: **X. Lyu:** None. **S. Lyu:** None. **G. Wang:** None. **Y. Zhang:** None.

Poster

PSTR070. Glia-Neuron Interaction

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.09/D31

Topic: B.09. Glial Mechanisms

Support: HBI Graduate Recruitment Scholarship
Canadian Institutes for Health Research Project Grant

Title: Semaphorin3fa in Müller Glia driven repair

Authors: *K. SHEWCHUK[1], J. GONZALES[1], S. MCFARLANE[2];
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Abstract: The retina is a highly organized tissue found at the back of the eye, and contains visual circuits that convert light energy into visual information. Retinal degeneration is characterised by the death of specific retinal cell types and is followed by vision loss, which is permanent in humans. This permanent vision loss is accompanied by decrease in quality of life and higher risk for depression and anxiety. Müller glia in the mammalian retina produce scarring in response to damage and disease, without replacing lost cells. In the zebrafish retina, however, Müller glia proliferate and produce new cells to restore visual circuits and vision. It is believed

that the difference in the regenerative capacity of Müller glia lies with proteins and signaling pathways that are different between the zebrafish and mammalian retina. Here, we investigated the role of Semaphorin3fa (Sema3fa), an axon guidance molecule, in the regenerative capacity of Müller glia in the zebrafish retina. We combined a light injury method to induce photoreceptor death in the zebrafish eye with a previously characterized zebrafish CRISPR line, *sema3fa*^{ca304ca304}, null for Sema3fa. To assess the Müller glia injury response, we used EdU labelling for proliferation, as well as immunohistochemistry and mRNA visualization and measurement techniques to investigate changes in key response genes. We observed *sema3fa* mRNA in resting Müller glia of the uninjured larval eye. Via RT-qPCR, we observed a downregulation of *sema3fa* mRNA in the zebrafish larval retina from 24-96 hours post-injury, suggesting a role of this protein in Müller glia injury response. In the absence of Sema3fa, the proliferative response to injury was prolonged as compared to wild type as illustrated through EdU labelling. Similarly, RT-qPCR analysis shows downregulated expression of *ascl1a*, an essential gene in Müller glia reprogramming and proliferation, at 96 hours post injury in mutant fish as compared to wild type. These findings point to a potential role of Semaphorin3fa signaling in Müller glia driven repair, specifically in the proliferative response. Grant Support: Hotchkiss Brain Institute Recruitment Award to K.S., Canadian Institutes for Health Research Project Grant.

Disclosures: **K. Shewchuk:** None. **J. Gonzales:** None. **S. McFarlane:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.10/D32

Topic: B.09. Glial Mechanisms

Title: It Takes Two—Or Three: Comparing Human Pluripotent Stem Cell Derived Glia-Neuron Co-Cultures to Neuron Monoculture Under Basal and Injury Conditions

Authors: J.-Y. WANG[1], J. CHAN[1], ***M. SCHMIDT**[1], A. C. EAVES[1,2], S. A. LOUIS[1], E. KNOCK[1,3];
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Abstract: Current advances in the field allow for efficient generation of pure neuron, astrocyte, and microglia cultures from human pluripotent stem cells (hPSCs). However, these monocultures lack physiologically important glia-neuron interactions. We created a protocol to co-culture neurons with astrocytes and microglia to assess the impact of glia co-culture on neuronal morphology and recovery under basal and injury conditions. We generated hPSC-derived forebrain neurons, astrocytes, and microglia using the STEMdiff™ Forebrain Neuron, Astrocyte, and Microglia culture systems, respectively. First, we maintained co-cultures of astrocytes with forebrain neurons for one week at a 2:1 or 1:1 ratio using STEMdiff™ Forebrain Neuron

Maturation Medium. We evaluated the effect of astrocyte presence on neuronal phenotypes by measuring the neurite length and number of MAP2-positive cells in co-cultures versus monocultures. Next, we established a tri-culture model containing hPSC-derived forebrain neurons, astrocytes, and microglia in BrainPhys™-based hPSC Neuronal Medium with STEMdiff™ Microglia Supplement 2. To assess cell migration in response to injury, we utilized the Incucyte® 96-well WoundMaker Tool to scratch the mono-, co-, and tri-cultures. Neuronal recovery was analyzed after 48 hours by measuring the percentage of the scratched area covered by of GFAP+ astrocytes, βIIITUB+ neurons, and GFP-fluorescent microglia. After one week of neuron-astrocyte co-culture, we observed a non-significant increase in MAP2+ forebrain neurons and a significant 1.26 ± 0.09-fold increase in neurite length (mean ± SEM, normalized to control; control n = 4; co-culture n = 5; p = 0.04) for co-cultured neurons compared to the neuron monoculture control. These data indicate that co-culture with astrocytes could improve the maturation of forebrain neurons. Immediately after scratch with the WoundMaker, the neuron-astrocyte co-culture and tri-culture displayed less post-injury cell detachment compared to the neuron monoculture and neuron-microglia co-culture. Preliminary results also suggested that increasing the quantity of microglia in the tri-culture may positively correlate with an increase in the resulting number βIIITUB+ neurons in the area of injury. These results demonstrate that pure populations of astrocytes, neurons, and microglia can be cultured together to display developed neuronal phenotypes and functional properties compared to neuron monocultures.

Disclosures: **J. Wang:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **J. Chan:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **M. Schmidt:** 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

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.11/D33

Topic: B.09. Glial Mechanisms

Title: Glial Dysregulation of Sympathetic Ganglia in Traumatic Brain Injury

Authors: *J. OH[1], K. WHANG[2];
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Abstract: Traumatic brain injury (TBI) is clinically well-known to be associated with systemic autonomic dysfunction. The exact mechanisms of acute phase of TBI with secondary brain damage is still under scientific investigations. Of many mechanisms speculated, the glial response of autonomic ganglia was the target of our interests because the dysregulation of

autonomic system consequently results in a massive inflammatory damage directly to both injured and normal brain tissues with uncontrolled intracranial pressure and cardiac dysfunctions. Rodent TBI model was produced by a controlled cortical injury through external force. The tissue samples acquired from the acute phase of the injured brain and stellate ganglia were studied with immunofluorescent and immunohistochemical imaging analysis as well as biochemical experiments such as western blotting and semi-quantitative real-time polymerase chain reaction (qPCR). The activation of glial cells in stellate ganglion was markedly noted along with the gliosis of acutely injured brain tissues. These findings were demonstrated by glial fibrillary acidic protein (GFAP) with a substantial increase in the TBI tissue specimens compared with the sham controls. The immunological changes of IL-1beta and TNF-alpha protein expressions were strongly noted in the TBI models. In sum, one of the key cellular mechanisms underlying TBI-induced autonomic dysregulation may involve the pathological responses of autonomic glial cells with abnormal inflammatory cytokine productions.

Disclosures: J. Oh: None. **K. Whang:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.12/D34

Topic: B.09. Glial Mechanisms

Support: Ann Hanley Neuroscience Fund (University of Kentucky)
NEU STAR, Department of Neurosurgery (University of Kentucky)
BRAIN Alliance
Indiana State Department of Health (ITSCBIRF, Indiana)

Title: Profiling peripheral glial cells from intact and injured human nerves for grafting in the central nervous system

Authors: *G. I. APARICIO[1], J. E. QUINTERO[1], L. DENG[2], K. WANCZYK[3], M. MURPHY[3], G. A. GERHARDT[1], C. G. VAN HORNE[1], P. V. MONJE[1];
[1]Dept. of Neurosurg., Univ. of Kentucky, Lexington, KY; [2]Dept. of Neurolog. Surgery, Stark Inst., Indianapolis, IN; [3]Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: The unique pro-regenerative capability of peripheral nervous system (PNS) cells, including repair Schwann cells (SCs) from injured nerves, has been exploited clinically in cell transplantation therapies to treat central nervous system (CNS) trauma and neurodegenerative diseases. However, the characteristics of peripheral nerve cells has not yet been addressed thoroughly in humans. Therefore, the goal of this study was to identify specific markers able to reveal the identity and stage of differentiation of cells from intact and injured human nerves before and after implantation within CNS tissues. To study injury-associated changes in the expression of SC markers, we developed an in vitro model of human nerve degeneration to be

compared with injured nerve grafts and brain tissues from participants enrolled in a nerve transplantation clinical trial for Parkinson's disease (NCT02369003, NCT05377281). Overall, our results confirmed the value of using antibodies against S100β, myelin protein zero (MPZ), periaxin (PRX), NGFR, GFAP, and Sox10, alone and in combination with axonal markers and myelin-selective fluorophores, to identify mature (intact) and repair (injured) human SCs in relationship to axons, myelin, and nonglial cells. In particular, our histological analysis revealed that: (1) NGFR was a reliable marker to discriminate PNS-derived cells, including repair SCs, from CNS neurons and glial cells; (2) S100B, GFAP, and Sox10 were useful to specifically identify SCs within intact and injured nerve tissues, with the caveat that they also revealed glial populations in the CNS (astrocytes and oligodendrocytes); and (3) MPZ and PRX were equally useful to identify human myelin sheaths derived from SCs rather than oligodendrocytes. To conclude, the above-mentioned markers can be used in different combinations to reveal grafted PNS cells, mainly SCs, in the human CNS to study their survival, differentiation, and relationship to host tissue.

Disclosures: G.I. Aparicio: None. **J.E. Quintero:** None. **L. Deng:** None. **K. Wanczyk:** None. **M. Murphy:** None. **G.A. Gerhardt:** None. **C.G. van Horne:** None. **P.V. Monje:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

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Program #/Poster #: PSTR070.13/D35

Topic: B.09. Glial Mechanisms

Support: NIH/NINDS R01NS109077
NIH/NIDA R01DA048822
NIH/NIHMS R01MH119355

Title: Altered calcium signaling in Bergmann glia contributes to Spinocerebellar ataxia type-1

Authors: *C. PEREZ DE NANCLARES, J. A. NORIEGA-PRIETO, F. E. LABRADA-MONCADA, M. CVETANOVIC, A. ARAQUE, P. KOFUJI;
Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease caused by an abnormal expansion of glutamine (Q) encoding CAG repeats in the *ATAXIN1* (*ATXN1*) gene and characterized by progressive cerebellar ataxia, dysarthria, and eventual deterioration of bulbar functions. SCA1 shows severe degeneration of cerebellar Purkinje cells (PCs) and activation of Bergmann glia (BG), a type of astroglia closely associated with PCs. Using electrophysiological recordings, confocal imaging and chemo-genetic approaches, we have investigated the intrinsic electrical and synaptic properties of PCs and the physiological properties of BG in a SCA1 mouse model expressing mutant ATXN1 only in PCs. Specifically, PCs in SCA1 mice exhibited a lower spontaneous firing rate and larger afterhyperpolarization currents (IAHP) compared to

wildtype mice, while the properties of synaptic inputs remained unaffected. On the other hand, BG in SCA1 mice displayed calcium hyperactivity and gliotransmission, characterized by an increased frequency of NMDAR-mediated slow inward currents (SICs) in PCs. Restoring BG calcium hyperexcitability in SCA1 mice by introducing the calcium chelator BAPTA resulted in the normalization of IAHP and spontaneous firing rate in PCs, bringing them to levels similar to those observed in wildtype mice. Furthermore, inducing BG hyperactivity in wildtype mice by activating BG expressing Gq-DREADDs replicated the pathological phenotype of PCs seen in SCA1, including enhanced IAHP and reduced spontaneous firing rate. These findings suggest that the intrinsic electrical properties of PCs, rather than their synaptic properties, are altered in SCA1 mice, and this alteration is associated with the hyperexcitability of BG. Notably, the prevention of BG hyperexcitability in SCA1 mice and the induction of BG hyperexcitability in wildtype mice respectively halted and replicated the pathological electrophysiological phenotype of PCs. Consequently, BG emerges as a crucial factor contributing to the dysfunction of the electrical intrinsic properties of PCs in SCA1 mice, indicating their potential as therapeutic targets for addressing spinocerebellar ataxia type 1.

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Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.14/D37

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01DA041208
NIH Grant MH083728
NIH Grant MH094268

Title: Role of astrocyte μ opioid receptors in negative valence states

Authors: *M. V. PLETNIKOV, S. THOMPSON, S. HUSEYNOV, K. MURLANOVA, O. PLETNIKOV;
Physiol. and Biophysics, State Univ. of New York, Univ. at Buffalo, Buffalo, NY

Abstract: Title: Role of astrocyte μ opioid receptors in negative valence states
Stephen Thompson, Shovqi Huseynov, Kateryna Murlanova, Olga Pletnikov, and Mikhail V. Pletnikov
Department of Physiology and Biophysics, State University of New York, University at Buffalo,Buffalo, NY
Key words: Astrocyte, Opioid, Emotion
Opiates make up a large fraction of the most effective analgesics commonly prescribed to patients, and the high probability of addition presents a major concern when administered,

especially over a long-term. Our current body of work seeks to understand the role of astrocyte mu opioid receptors in regulating the effects of protracted opiate abstinence on neuronal activity in a brain-region and sex-dependent manner. Using fiber photometry, we study temporal dynamics of neural activity in freely behaving animals. Furthermore, using targeted intracranial injections of astrocyte specific Cre-expressing AAV to the brain of *Oprm1*$^{fl/fl}$ mice, we aim to uncover the region-specific mechanisms whereby astrocyte mu opioid receptors are involved in protracted abstinence-produced negative valence behaviors in male and female mice. A better understanding of the neuronal responses to altered functions of astrocyte opioid signaling may help develop new therapies to mitigate physiological responses during abstinence and associated negative states.

Disclosures: M.V. Pletnikov: None. **S. Thompson:** None. **S. Huseynov:** None. **K. Murlanova:** None. **O. Pletnikov:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

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Program #/Poster #: PSTR070.15/D38

Topic: B.09. Glial Mechanisms

Support: Robert J. and Nancy D. Carney Endowment
Carney Institute Howard Reisman '76 Family Graduate Fellowship Fund
Carney Institute Mahoney Fund

Title: Investigating the Neuroprotective Mechanisms of Oligodendroglia During Wallerian Degeneration

Authors: *M. MCQUILLAN[1], G. MOLICA[2], L. CEUS[4], S. E. RAISSI[5], C. CALL[3], S. R. MAYORAL[2];
[1]Neurosci., [2]Brown Univ., [3]Brown Univ., Providence, RI; [4]Rutgers Univ., New Brunswick, NJ; [5]Neurol., UCSF, San Francisco, CA

Abstract: Neurodegenerative diseases affect millions of people worldwide, however, they remain a major scientific problem as little progress has been made on their prevention and potential cure. Myelin, the compact, lipid-rich sheath that insulates neuronal axons, has now been implicated in having a neuroprotective role in multiple mouse models of neurodegenerative diseases including Multiple Sclerosis and Alzheimer's Disease. However, the mechanism of this protection and the role both myelin and oligodendrocytes (OLs), the myelin-producing cells of the CNS, play in this process, are still unknown. This is in part due to the challenge of studying OLs and myelin-specific axonal effects, as current methods involve administration of toxins or cell ablation, both of which are temporary and produce their own injury and inflammation to the system. To circumvent this problem, we use a genetic approach where removal of a growth factor receptor (PDGFRa) from oligodendrocyte precursor cells (OPCs) restricts their

developmental occupation of certain regions of the CNS including the optic nerves. This results in a unique and robust phenotype, where OPCs occupy, differentiate into OLs, and myelinate only the posterior portion of the optic nerves (ONs). Using this model, we show that the presence of myelin delays Wallerian Degeneration (WD), a well-characterized type of axon degeneration that follows transection, as longer axonal fragments are present in the myelinated regions of these nerves compared to their unmyelinated counterparts six days post injury. This is further supported by electron microscopy, where we find fewer axons present in unmyelinated optic nerves following transection, again suggesting that these axons degenerate faster when no myelin is present. Preliminary data has also shown *in vitro* changes in kinase activity within the WD pathway, thereby revealing a potential mechanism for how these axonal protective effects occur. Taken together, these data suggest that myelin plays an important role in delaying degeneration and will provide important insights into axonal protection, which has the potential to inform therapeutic approaches for neurodegenerative diseases.

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Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.16/D39

Topic: B.09. Glial Mechanisms

Support: National Eye Institute U24 EY029903
Stanford Vision Research Core P30 EY026877
Research to Prevent Blindness
Gilbert Family Foundation

Title: Translational Profiling of Reactive Muller Glia Following Cell type-specific Retinal Injury

Authors: *M. ASHOURI[1], M. B. BHUCKORY[2], X. XIA[1], M. NAHMOU[3], C. TSIEN[1], E. G. CAMERON[4], S. WANG[1], D. PALANKER[1], J. GOLDBERG[2];
[2]Ophthalmology, [1]Stanford, Palo Alto, CA; [3]Stanford Univ., Stanford Univ., Mountain View, CA; [4]Stanford Univ., Stanford Univ., Palo Alto, CA

Abstract: Translational Profiling of Reactive Muller Glia Following Cell type-specific Retinal Injury Purpose: Muller glia (MG) respond to retinal injuries, such as traumatic optic neuropathy or retinal detachment, through a process known as reactive gliosis. Reactive glia have both neuroprotective and neurotoxic functions depending on the mechanism and location of injury. Although RGC- and photoreceptor-specific diseases can both cause reactive gliosis, the specific pathways affected in Muller glia are unknown. Unraveling these cellular responses would allow us to more specifically design therapies to preserve retinal function in the face of disease. Methods: A modified, tagged RPL22 protein was expressed in MG using a highly specific AAV-

8 virus via subretinal injection in early postnatal mice. At postnatal day 21, optic nerve crush (ONC) or retinal detachment (RD) were performed to model retinal ganglion cell (RGC) and photoreceptor (PR) death, respectively, and verified via OCT. Translational changes within Muller glia were assessed in these two methods of retinal injury by isolating the tagged ribosomal complex and its actively translating RNA 3 days later. We then sequenced and analyzed the Muller glia RNA for translational changes associated with glial reactivity following ONC and RD injuries in vivo. Results: Retinal imaging revealed successful transduction of MG with AAV-8/RPL22-HA in vivo. At postnatal day 3, peak GFAP expression was observed by immunofluorescence. OCT imaging revealed that the retina remained detached until 3 days after hyaluronic acid injection. Comparison of translational changes in ONC/RD injury models to non-injury control samples revealed major differences in actively translating mRNAs between the RGC- and photoreceptor-specific injuries within Muller glia. Conclusion: Muller glia uniquely stratify all layers of the retina, including photoreceptors and RGCs, and respond to injuries to either cell type through reactive gliosis. The differential response to either type of injury provides insight into glial regulation and will inform future injury-specific glial therapeutics.

Disclosures: **M. Ashouri:** None. **M.B. Bhuckory:** None. **X. Xia:** None. **M. Nahmou:** None. **C. Tsien:** None. **E.G. Cameron:** None. **S. Wang:** None. **D. Palanker:** None. **J. Goldberg:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

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Program #/Poster #: PSTR070.17/D40

Topic: B.09. Glial Mechanisms

Support: NEI P30EY029220
Research to Prevent Blindness

Title: In vitro calcium imaging reveals multiple attributes of glial activity during light-induced retinal degeneration

Authors: *S. T. WALSTON;
Ophthalmology, USC, Los Angeles, CA

Abstract: Introduction: Prolonged ocular exposure to bright light has been shown to cause light-induced retinal degeneration (LIRD) in vivo. This investigation demonstrates the utility of in vitro calcium imaging and electrophysiology to track the real-time progression of LIRD by monitoring glial and neural activity. Glial cells are non-neuronal cells that perform several functions that include responding to injury, regulating the release neurotrophic factors, recycling neurotransmitters, controlling blood flow, and modulating neural activity. Glial cells of the retina include Müller cells, astrocytes, and microglia. **Methods:** In vitro calcium imaging with the Fluo4-AM dye was used to monitor retinal glial cell activity in the Royal College of Surgeons

(RCS) rat model of retinal degeneration. Wholemount retina was incubated with the dye in oxygenated Ames' Medium and then placed ganglion cell side down on a glass multielectrode array. A 600µm diameter region of the retina was stimulated with bright light (446 - 486nm) from an LED for 60 minutes. Real-time glial calcium activity was imaged with an inverted microscope, while retinal ganglion cell activity was monitored via electrical recording with 30µm-diameter titanium nitride microelectrodes. **Results:** In the retina, the Fluo4-AM calcium dye preferentially loads into Müller cells and astrocytes. Prolonged bright blue light stimulation evokes calcium transients in Müller glial cells. The frequency of calcium transients increases throughout the stimulation period. A sustained elevation of calcium fluorescence is observed in astrocytes. During the stimulation, glial and neural activity abruptly terminates when a large calcium wave radiates outward from the stimulated region and blood vessels constrict. This is immediately followed by retinal swelling (edema). Regions of the retina distant from the stimulated area appear unaffected. **Conclusion:** This investigation demonstrates that in vitro calcium imaging and electrophysiology with wholemount retina can be used to reveal multiple attributes of glial and neural activity in response to noxious light stimuli. This experimental platform may be useful for evaluating glial and neural responses to various stimulus conditions and for evaluating the real-time effect of therapeutic interventions.

Disclosures: S.T. Walston: None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.18/D41

Topic: B.09. Glial Mechanisms

Support: R01NS110694

Title: Striatal $GFAP^+$ astrocytes and their association with white matter fascicles in a mouse model of Huntington's disease

Authors: *T. G. BROWN, M. THAYER, E. REID, J. VANTREECK, R. GOMEZ-PASTOR; Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Huntington's disease (HD) is a neurodegenerative disease that primarily affects the striatum, a brain region that controls movement and some forms of cognition, and manifests as motor, cognitive, and psychiatric impairments, including apathy. Neuronal dysfunction and loss in HD is accompanied by increased astrocyte density and astrocyte pathology. Astrocytes are a heterogeneous population classified into multiple subtypes depending on the expression of different gene markers. Studying whether mutant Huntingtin (HTT) alters specific subtypes of astrocytes is necessary to understand their relative contribution to HD. Here, we studied whether astrocytes expressing glial fibrillary acidic protein (GFAP), a subset of striatal astrocytes, were differentially altered in HD. Typically $GFAP^+$ astrocytes indicate a reactive phenotype in

neurodegenerative diseases. As hypothesized, we showed that the abundance of $GFAP^+$ astrocytes increased in HD mice compared to WT, coinciding with increased HTT aggregation. Interestingly, $GFAP^+$ astrocytes appeared in spatial clusters in the dorsomedial striatum, a region associated with goal-directed behaviors. In addition, these $GFAP^+$ astrocytes were found in areas of low HTT aggregate load in HD mice and in association with white matter fascicles in both WT and HD mice. In rodents, white matter fascicles passing through the striatum can come from many brain regions and we used neuronal tracing experiments to determine the origin of $GFAP^+$ fascicles. We found that many of these fascicles originate in the secondary motor cortex, a region within the medial prefrontal cortex. Both the medial prefrontal cortex and white matter atrophy have been shown to be associated with apathy in the general population. It is possible that $GFAP^+$ astrocyte accumulation on white matter fascicles may be the underlying cause of apathy in HD patients and the unique spatial arrangement of striatal $GFAP^+$ astrocytes may offer new insights into the function of these specific astrocytes and their potential implications in HD pathology and symptomology.

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Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.19/D42

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: STI2030-Major Projects of China (2021ZD0200900)
National Key Research and Development Program of China (2022YFC3400100)
Shanghai Municipal Science and Technology Major Project (2018SHZDZX05)
Shanghai 2023 Special Biopharmaceutical Science and Technology Support Projects (23S41900300)

Title: Treatment of neurodegenerative disorders by astrocyte-specific overexpression of TMEM164

Authors: *L. ZHANG, Z. JIA, Z. XU, H. ZHOU;
Chinese Acad. of Sci. Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China

Abstract: Neuroinflammatory microglia secrete cytokines IL-1α, TNF, and C1q to induce neurotoxic reactive astrocytes, which are considered to be one of the major causes of neuronal death for many neurodegenerative diseases. However, the intrinsic key regulators underlying neurotoxic reactive astrocytes induction are unknown. Here, we identified transmembrane

protein TMEM164 as an early response intrinsic factor that regulates neurotoxic astrocyte reactivity through co-profiling of bulk RNA-sequencing (RNA-seq) of reactive astrocytes and single-nucleus RNA-sequencing (snRNA-seq) datasets of patients with different neurodegenerative disorders. TMEM164 overexpression inhibited the induction of neurotoxic reactive astrocytes, maintained normal astrocytic functions, and suppressed neurotoxic reactive astrocyte-mediated neuronal death in both mouse and human astrocytes. Mechanistically, TMEM164 overexpression suppressed neuronal death by decreasing the secretion of neurotoxic saturated lipids. *In vivo*, we demonstrated that AAV-mediated astrocyte-specific TMEM164 overexpression prevented the induction of neurotoxic reactive astrocytes, dopaminergic neuronal loss and motor deficits in a Parkinson's disease (PD) model. Notably, brain-wide astrocyte-specific TMEM164 overexpression prevented the induction of neurotoxic reactive astrocytes, Aβ deposition, neurodegeneration, and memory decline in the 5XFAD Alzheimer's disease (AD) mouse model, implying that TMEM164 is a potential therapeutic target for diverse neurodegenerative diseases.

Disclosures: **L. Zhang:** None. **Z. Jia:** None. **Z. Xu:** None. **H. Zhou:** None.

Poster

PSTR070. Glia-Neuron Interaction

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Program #/Poster #: PSTR070.20/D43

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Multiple Sclerosis Society RG 1807-32053

Title: Decreased locomotion in response to peripheral cytokine injection is partially controlled by astrocyte transforming growth factor beta associated kinase (TAK1).

Authors: *S. KRAUKLIS[1], A. Y. LOUIE[2], D. B. MCKIM[3], A. STEELMAN[3];
[1]Div. of Nutritional Sci., Univ. of Illinois At Urbana-Champaign, Urbana, IL; [2]Neurosci. Program, [3]Dept. of Animal Sci., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Systemic inflammation resulting from infection occurring outside of the central nervous system induces behavior modifications including cognitive impairment, anxiety, lethargy and depression and can accelerate the progression of many neurological disorders and diseases. Upregulation TNF and IL-1, specifically, have been shown to promote sickness behaviors, but inhibition of either individually following a peripheral immune challenge is not sufficient to ameliorate all symptomology. Astrocyte endfeet extend into the basement membrane of the peri-meningeal space and the neurovascular unit, responding to peripheral signals, modulating blood brain barrier permeability, and leukocyte access to the central nervous system. Transforming growth factor beta associated kinase (Map3k7 or Tak1) is a key mediator of immune signal transduction. We previously found that inhibition of TAK1 suppressed chemokine production from TNF/IL-1 stimulated primary astrocytes and that conditional

deletion of TAK1 suppressed experimental autoimmune encephalomyelitis. Here, we questioned whether astrocyte TAK1 was involved in promoting sickness behaviors following peripheral cytokine injection. Specifically, $Tak1^{fl/fl}$ and $GfapCre^{ERT2}$:$Tak1^{fl/fl}$ male and female mice aged 5-6 weeks were treated with tamoxifen (5mg/day by oral gavage) for 5 days to induce Tak1 deletion. After a two week washout period, mice were injected with either sterile saline or recombinant cytokines (TNF/IL-1β; 500ng each). Home cage locomotion activity was recorded for 24 hours and resulting videos and analyzed using Noldus Ethovision XT. Mice were euthanized 24 hours after injection then blood, prefrontal cortex, hippocampus, and cerebellar tissues were isolated to measure changes in inflammatory markers by ELISA and RT-qPCR. Initial characterization of behavior showed that deletion of Tak1 in astrocytes did not affect behaviors of unchallenged control mice. Injection of cytokines suppressed locomotion in wild-type C57BL/6 mice. As with wild-type mice, $Tak1^{fl/fl}$ displayed significantly less movement in the 8 hours following cytokine injection compared to the saline injected groups. Interestingly, deletion of Tak1 in astrocytes ameliorated cytokine induced changes to locomotion, such that changes in their locomotion were only different from the saline injected groups during the first 2 hours. Loss of TAK1 in astrocytes was associated with a decrease in the duration of severe sickness behavior following cytokine injection, supporting existing evidence of the role of astrocytes in affecting the CNS response to peripheral inflammation.

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Poster

PSTR070. Glia-Neuron Interaction

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Topic: B.09. Glial Mechanisms

Support: NIA grant R01AG055545
NIA grant R56AG077814

Title: Contribution of PSC specific secreted factors to NMJ, muscle, and motor neuron aging

Authors: *M. AVILA[1], R. HASTINGS[2], E. SUNEBY[2], G. VALDEZ[2,3,4];
[1]Pathobiology Grad. Program, [2]Mol. Biology, Cell Biol. and Biochem., [3]Ctr. for Translational Neurosci., [4]Dept. of Neurology, Warren Alpert Med. Sch., Brown Univ., Providence, RI

Abstract: Degeneration of the neuromuscular junction (NMJ) in aging is associated with a decline in muscle strength and function shown to precede muscle atrophy. Age-associated changes to the presynaptic and postsynaptic regions of the NMJ have been well characterized. Conversely, little is known about the effect of aging on perisynaptic Schwann cells (PSCs), the synaptic glia at NMJs. Our lab has shown that PSCs remain at the NMJ of aged mice but display a range of cellular alterations in both middle and old age. Here, we show that PSCs from young and aged mice present with changes in expression of genes and activation of pathways associated

with inflammation, cell signaling, and phagocytosis. These findings suggest that PSCs in aged animals may become pro-inflammatory, more phagocytic, and recruit other cells to NMJs succumbing to aging. Among altered genes that may specify these different actions of PSCs in old age is the C-C motif chemokine ligand 7 (Ccl7). Ccl7 is a pluripotent chemokine that binds to several receptors present in PSCs, myelinating Schwann cells, and immune cells including macrophages. Bulk RNAseq analysis revealed that Ccl7 expression is higher in PSCs from aged animals compared to PSCs from young animals. We also found Ccl7 protein increased in aged PSCs using immunohistochemistry. In ongoing experiments, we are assessing whether Ccl7 plays important roles in PSCs and NMJ aging. We are also examining other PSC-specific secreted factors on aging of NMJs, muscles and motor neurons.

Disclosures: M. Avila: None. **R. Hastings:** None. **E. Suneby:** None. **G. Valdez:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.22/D45

Topic: B.09. Glial Mechanisms

Support: NIA grant # R21AG079550

Title: Immune System Maturity in Mice Alters the Behavior of Glia and T-Cells in Alzheimer's Disease

Authors: *D. SHAPIRO[1,2], J. PACIA[3], M. HASAN[3], M. KANTOROVICH[1], L. BEURA[3], G. VALDEZ[2];
[2]Mol. Biology, Cell Biology, and Biochem., [3]Mol. Microbiology and Immunol., [1]Brown Univ., Providence, RI

Abstract: Many discoveries in mouse models of Alzheimer’s Disease (AD) have not translated to successful treatments in human patients. One possible factor for this failure may be that mouse models of AD are studied in ultra-hygienic specific pathogen free environment, which keeps the immune system of such animals in a naïve, immature, state. This is important to consider because humans develop a mature immune system that also changes during the course of AD-related pathology. Thus, it may be necessary to study mouse models of AD with matured immune systems to discover treatments that translate to human patients with AD. To this end, we have optimized a protocol to study AD mouse models exposed to pathogens and microbes found in the wild, herein described as “dirty” mice. This treatment protocol yielded mice which exhibited higher levels of antigen experience and terminal differentiation among their T-cell population. These changes in the dirty mice correspond to greater immune maturity and are closer to that which is seen in the human immune system. Importantly, we are finding that the brain of dirty AD mice exhibits important differences compared to clean littermates (mice housed in a barrier facility). These include higher levels of peripheral immune infiltration and

greater levels of gliosis in dirty compared to clean AD mice. Additional experiments are being conducted to examine the effect of these changes on synapses and cognitive function in AD mouse models.

Disclosures: **D. Shapiro:** None. **J. Pacia:** None. **M. Hasan:** None. **M. Kantorovich:** None. **L. Beura:** None. **G. Valdez:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.23/D46

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

Title: Functional characterization of healthy and disease-related 3D neurospheres assembled using iPSC-derived neurons and astrocytes

Authors: *O. SIRENKO[1], C. CRITTENDEN[2], A. LIM[2], R. K. FIENE[3], S. SCHACHTELE[4], C. CARLSON[5];
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Abstract: Neural 3D spheroids are a rapidly developing technology with great potential for understanding brain development and neuronal diseases. In this study, we demonstrate an efficient and modular approach for creating disease-specific neurospheres using defined combinations of fully differentiated iPSC-derived neural cells in tri-culture, including glutamatergic neurons, GABAergic neurons, and astrocytes. For disease modelling of epilepsy phenotypes, we used two different genetically modified GABAergic neurons (SCN1A KO or KCNT1 P924L mutation) and their isogenic pairs as matched controls. The *SCN1A* gene encodes the alpha subunit of the sodium channel NaV1.1 and it is the major gene implicated in Dravet Syndrome, a severe childhood *epilepsy*. The *KCNT1* gene encodes a potassium channel and the P924L mutation is linked to an early-onset epileptic encephalopathy. For Alzheimer misease modelling we used mutations of several isotypes of the ApoE gene.
We monitored morphology and functional activity (Ca^{2+} oscillations) of the neurospheres after 3 weeks in culture. The microtissues were also analyzed by confocal fluorescence imaging for cell organization and expression of neuronal markers (TUJ1) and astrocytes (GFAP). The calcium assay was performed on a FLIPR instrument capable of fast kinetic recordings using a calcium-sensitive dye and oscillation patterns were analyzed for peak frequency, amplitude, width, & spacing. Different baseline oscillation patterns were observed between control and disease neurospheres, however within each group calcium kinetics and patterns were highly consistent. For pharmacological characterization of the control and diseased phenotypes, we used a panel of 14 compounds, including selected molecules that affect GABA, AMPA, NMDA, sodium and potassium channels, dopamine receptors, as well as select neuroactive and neurotoxic substances. The functional responses demonstrated the predicted effects based on mode of action, consistent

across control and disease model 3D neurospheres. Moderately increased excitability was observed for mutated epilepsy phenotypes, showing in both, in the baseline pattern, also in the elevated responses to stimulating agents. In contrast, decreased activities were observed in Alzheimer-related ApoE 4/4 mutants, while the phenotype was reversed by addition of drugs used for treatment of Alzheimer disease memantine and donepezil. This biological system of 3D neurospheres paired with high-content imaging and detailed analysis of calcium oscillations demonstrates a promising tool for disease modeling and compound testing.

Disclosures: **O. Sirenko:** A. Employment/Salary (full or part-time):; full time, Molecular Devices, LLC. **C. Crittenden:** A. Employment/Salary (full or part-time):; full time, Molecular Devices, LLC. **A. Lim:** A. Employment/Salary (full or part-time):; full time, Molecular Devices, LLC. **R.K. Fiene:** A. Employment/Salary (full or part-time):; full time, Fujifilm. **S. Schachtele:** A. Employment/Salary (full or part-time):; full time, Fujifilm. **C. Carlson:** A. Employment/Salary (full or part-time):; full time, Fujifilm.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.24/D47

Topic: B.09. Glial Mechanisms

Support: Moonshots for Unicorns
Families of SCN2A

Title: Unraveling the Role of Glia in PGAP3-CDG Disease: A Cutting-Edge In Vitro Modeling Approach for Therapeutic Testing

Authors: *J. A. SIERRA DELGADO[1], M. GANJIBAKHSH[1], A. KALEEM[1], S. SINHA RAY[1], X. ZHANG[1], S. B. LIKHITE[1], K. C. MEYER[1,2];
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Abstract: PGAP3-CDG, a fatal autosomal recessive disorder, belongs to the group of hyperphosphatasia with mental retardation syndromes. Loss of PGAP3 disrupts GPI anchor biosynthesis, resulting in secondary stress responses and decreased GPI-Anchored Proteins. Phenotypically, PGAP3-CDG patients exhibit a wide range of characteristics, including developmental delay, intellectual disability, hypotonia, facial dysmorphism, and elevated serum alkaline phosphatase. Seizures and gastrointestinal symptoms are common. Phenotype-genotype correlation remains unclear. The underlying mechanisms through which PGAP3 mutations give rise to the diverse range of phenotypes remain poorly comprehended. Limited knowledge exists regarding the effects of GPI-anchored protein loss and the expression of PGAP3 in neurons, as well as the involvement of glial cells, particularly astrocytes, in the progression and mechanisms of the disease. To address this, we used a direct reprogramming method to generate Neural

Progenitor Cells (iNPCs) from primary fibroblasts derived from PGAP3-CDG patients. We then differentiated the iNPCs into induced astrocytes (iAs) to evaluate classic stress markers such as mitochondrial and endoplasmic reticulum stress commonly observed in neurological disease. Notably, PGAP3 iAs exhibited an unusual cellular morphology characterized by a condensed soma. Consequently, there was an atypical mitochondrial morphology characterized by a compact mitochondrial network. Based on this observation, we evaluated the mitochondrial activity profile of PGAP3 iAs using the Seahorse Bioscience XF96 Extracellular Flux Analyzer platform, finding significant changes in mitochondrial activity in both basal and ATP linked respiration. We also developed a co-culture system using healthy mouse GFP+ neurons in contact with the patient iAs. Using this system, we found that iAs induced a high degree of neuronal death. We then tested a vast array of compounds and medias on the PGAP3-CDG iAs, showing that copper compounds could partially rescue both the neuronal support as well as the metabolic phenotype. Additionally, to further study the effect of mutations in neurons, we generated induced neurons (iNs) from patient's fibroblasts and are currently evaluating patient specific phenotypes. These in vitro culture systems are a useful tool for testing of new therapeutic strategies in order to accelerate development of novel treatments.

Disclosures: **J.A. Sierra Delgado:** None. **M. Ganjibakhsh:** None. **A. Kaleem:** None. **S. Sinha Ray:** None. **X. Zhang:** None. **S.B. Likhite:** None. **K.C. Meyer:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.25/D48

Topic: B.09. Glial Mechanisms

Support: NIA grant # R01AG055545
NIA grant # R56AG077814

Title: Neuromuscular junction instability precedes muscle degeneration in a mouse model of Megf10-related myopathy

Authors: *D. JUROS[1], A. PENDRAGON[2], J. KAY[2], G. VALDEZ[1];
[1]Brown Univ., Providence, RI; [2]Duke Univ., Durham, NC

Abstract: The pathophysiology underlying many rare congenital myopathies is still poorly understood, posing an obstacle for treatment development. One such myopathy is Early-onset Myopathy, Areflexia, Respiratory Distress, and Dysphagia (EMARDD), which is caused by mutations in MEGF10. While research has focused on the role of Megf10 in muscle regeneration, published evidence suggests that impaired motor function in mice with Megf10 mutations precedes structural damage to muscle. Following published evidence of Megf10 expression at the neuromuscular junction (NMJ), we used immunohistochemistry to assess NMJ morphology in juvenile (1mo) and young adult (3mo) male and female mice with global

knockout of Megf10. Megf10 global knockout NMJs displayed a progressive increase in postsynaptic fragmentation, which is a structural change often associated with neuromuscular diseases and aging. This change to NMJ structure occurred despite the lack of muscle degeneration and regeneration observed in Megf10 global knockout mice at these ages. Further analysis of the NMJ via immunohistochemistry and electron microscopy showed that synaptic glia at the NMJ, perisynaptic Schwann cells (PSCs), in Megf10 global knockout mice aberrantly extend processes into the synaptic cleft and away from the NMJ, which are changes that may alter neurotransmission. We then used transgenic mice and molecular approaches to demonstrate that Megf10 is expressed by PSCs, which are specialized nonmyelinating Schwann cells that directly associate with the NMJ and regulate its formation, maintenance, and repair. To determine the role of Megf10 in PSCs, we knocked out Megf10 specifically in SOX10-producing cells which includes PSCs and other Schwann cells. Surprisingly, young adult mice with PSC-specific knockout of Megf10 had no change to the structure of the NMJ or its repair following nerve injury. This suggests that mutations in Megf10 in motor neurons and/or muscle cells, but not PSCs, impairs the stability of the NMJ, indirectly eliciting a regulatory response from PSCs. Together, these data identify the NMJ as a site of pathology in Megf10-related myopathy which is likely independent from the role of Megf10 in muscle regeneration and is not driven by direct alterations in PSC function. This information informs treatment development for EMARDD by identifying the NMJ as a new pathophysiological target.

Disclosures: **D. Juros:** None. **A. Pendragon:** None. **J. Kay:** None. **G. Valdez:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.26/D49

Topic: B.09. Glial Mechanisms

Support: NIA grant # R01AG055545
NIA grant # R56AG077814

Title: Apoe is a key mediator of microglia response to motor neurons in the spinal cord

Authors: *M. C. LOPES, R. W. CASTRO, G. VALDEZ;
Brown Univ., Providence, RI

Abstract: Spinal cord motor neurons are central for initiating and modulating all voluntary movements. The survival and proper function of motor neurons rely on a broad spectrum of supporting and modulatory functions carried out by spinal cord glia, particularly microglia. Microglia tile the CNS in an organized manner and constantly sense homeostatic disruptions allowing microglia to play essential roles in response to injury, disease, and aging. In the spinal cord, microglia aggregate around stressed motor neurons to reorganize the motor circuit and phagocytose debris. To date, however, the molecular mechanism that mediates these important

functions of spinal microglia remains unknown. Recent RNAseq analysis from our lab revealed apolipoprotein E (ApoE) and its receptor TREM2 to be among the most highly upregulated genes in aged motor neurons and microglia. These findings suggest that the ApoE pathway may play critical roles in mediating the interaction between motor neurons and microglia responding to stressors, such as aging, diseases, and injuries. To look into this possibility, we are comparing the response of spinal microglia to motor neurons with injured axons between ApoE null mice (ApoE KO) mice and wild-type (WT) mice. In an initial analysis, we found that microglia in ApoE KO animals appear to have a delayed response to injured motor neurons. The loss of ApoE also appears to reduce the phagocytic activity of spinal microglia around injured motor neurons. These and other ongoing experiments that include analysis of the motor circuitry will provide valuable insights into the role of the ApoE pathway in mediating the relationship between spinal microglia and motor neurons in normal and under stress conditions.

Disclosures: M.C. Lopes: None. **R.W. Castro:** None. **G. Valdez:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.27/D50

Topic: B.09. Glial Mechanisms

Support: NIA Grant R01AG055545
NIA Grant R56AG051501
NINDS Grant R21NS106313
NRSA T32 AG041688-11

Title: Aged synaptic Schwann cells acquire unique phagocytic and inflammatory properties

Authors: *R. HASTINGS[1], M. AVILA[2], D. JUROS[1], G. VALDEZ[1,3,4];
[1]Dept. of Mol. Biology, Cell Biol. and Biochem., [2]Pathobiology Grad. Program, [3]Ctr. for Translational Neurosci., [4]Dept. of Neurology, Warren Alpert Med. Sch., Brown Univ., Providence, RI

Abstract: Age-induced degeneration of the neuromuscular junction (NMJ) is associated with motor dysfunction and muscle wasting. While the impact of aging on the NMJ pre- and postsynapse is well-documented, little is known about the changes perisynaptic Schwann cells (PSCs), the synaptic glia of the NMJ, undergo during aging. Here, we first examined PSCs in young, middle-aged, and old mice using light and electron microscopy. We found that PSCs acquire age-associated cellular features suggesting an inflammatory state with phagocytic properties. Notably, we found that aged PSCs are more abundant in old compared to young mice, and that this hyper-proliferation is associated with defects in the pre- and post-synaptic regions of the NMJ. PSCs also encompass blebbed areas of the axon terminal and intercalate between the axon and the synaptic gutter. We next profiled the transcriptome of PSCs and other Schwann

cells (SCs) to identify mechanisms altered in aged PSCs. This analysis revealed that aged PSCs acquire a transcriptional pattern associated with exuberant phagocytosis that is absent in other SCs. It also showed that aged PSCs upregulate unique pro-inflammatory molecules compared to other aged SCs. These findings provide insights into cellular and molecular mechanisms that could be targeted in PSCs to stave-off the deleterious effects of aging on NMJs.

Disclosures: R. Hastings: None. **M. Avila:** None. **D. Juros:** None. **G. Valdez:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.28

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: China 32100759

Title: Schwann cell promotes macrophage recruitment through IL-17B/IL-17RB pathway in injured nerves

Authors: *Y. HUANG, Z. YING, L. WU;
China Agr. Univ., Beijing, China

Abstract: Schwann cell promotes macrophage recruitment through IL-17B/IL-17RB pathway in injured nerves
Authors *Yanju Huang1, Liwen Wu1, Zhengxin Ying1; 1 College of Biological Sciences, China Agricultural University, Beijing, China
Disclosures Yanju Huang: None. **Liwen Wu:** None. **Zhengxin Ying:** None.
Abstract Macrophage recruitment to the injured nerve initiates a cascade of events, including myelin debris clearance and nerve trophic factor secretion, that contribute to proper nerve tissue repair. Interleukin 17B (IL-17B) is a cytokine produced by various cells including T cells and macrophages. As a member of the IL-17 family, IL-17B plays a critical role in inflammation and immune responses. It remains unclear whether IL-17B affect macrophage recruitment, the regeneration and repair process of peripheral nerve. In this study, we compared *Mlkl*$^{-/-}$, *Sarm1*$^{-/-}$ mice, two strains with impaired myelin debris clearance, with WT mice, and identified IL-17B as a key regulator of macrophage recruitment. We next ectopically expressed IL-17B by injecting adeno-associated virus (AAV) under the control of MBP promoter in *Mlkl*$^{-/-}$ and S*arm1*$^{-/-}$ mice, the macrophage infiltration was significantly restored (33.3% ± 7.5 and 28.9% ± 4.7). The autocrine production of IL-17B by Schwann cell binds to IL-17 receptor B (IL-17RB) to active several key factors (CCL2 and CCL3) for recruiting macrophage, and mice with Schwann cell-specific deletion of IL-17B shows significantly decreased macrophage infiltration (33.7% ± 3.4), myelin clearance, and axon regeneration. Additionally, behavioral studies demonstrated a slower recovery in both motor and sensory abilities in injured *Il17b* and *Il17rb* KO mice (23.3% ± 8.8 and 18.75% ± 5.4, respectively). To explore the potential involvement of IL-17B/IL-17RB

activation in CNS injury, we investigated its expression levels in the optic nerve. In contrast to the sciatic nerve, we observed no substantial elevation of IL-17B levels following injury in the optic nerve. This finding suggests a correlation between the failure of myelin clearance in the CNS and reduced activation of IL-17B/IL-17RB signaling. In conclusion, our findings have identified an important role for Schwann cell autocrine of IL-17B during Wallerian degeneration and point to potential mechanistic targets for accelerating myelin clearance and improving demyelinating disease.

Disclosures: **Y. Huang:** None. **Z. Ying:** None. **L. Wu:** None.

Poster

PSTR070. Glia-Neuron Interaction

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.29/D51

Topic: B.09. Glial Mechanisms

Support: NIA Grant R01AG055545
NIA Grant R56AG077814

Title: Investigating the role of perisynaptic Schwann cells in ALS induced NMJ degeneration

Authors: *E. SUNEBY[1], T. TAETZSCH[2], D. JUROS[2], G. VALDEZ[2];
[1]Mol. Biology, Cell Biology, and Biochem. Grad. Program, [2]Brown Univ., Providence, RI

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating, adult-onset neurodegenerative disease that is characterized by the progressive loss of motor neurons. Patients suffer from muscle weakness, atrophy, and paralysis and the disease is typically fatal within five years of symptom onset due to respiratory failure. An attractive target for intervention in ALS is the neuromuscular junction (NMJ) which degenerates early and progressively throughout the disease. The NMJ is a tripartite synapse consisting of the axonal terminal of a motor neuron, a specialized region of the muscle fiber, and the synaptic glia termed perisynaptic Schwann cells (PSCs). PSCs are crucial for the maintenance and repair of the NMJ; however, little is known about their role in NMJ degeneration in ALS. To address this gap in knowledge, we have begun to characterize PSCs in mouse models of ALS prior to and during NMJ degeneration. So far we have discovered that PSCs exhibit morphological changes prior to NMJ degeneration using light and electron microscopy. We found that the number of PSCs per NMJ increases in ALS as the disease progresses. Additionally, a larger percentage of PSCs in ALS extends sprouts and forms bridges between NMJs, which are morphological changes characteristic of PSCs facilitating compensatory reinnervation following nerve injury in wildtype animals. We have also observed that PSCs in ALS extend processes into the synaptic cleft prior to retraction of the motor axon from the NMJ and fail to fully cap the NMJ. These initial findings suggest that PSCs participate in changes of the NMJ during the progression of ALS, highlighting the potential for targeting PSCs to preserve NMJs in ALS.

Disclosures: **E. Suneby:** None. **T. Taetzsch:** None. **D. Juros:** None. **G. Valdez:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.01/D52

Topic: B.10. Demyelinating Disorders

Support: Cure LBSL
Kennedy Krieger IDDRC NIH P50 HD103538

Title: Modeling LBSL and the cell-type specific effects of Dars2 deletion

Authors: *I. L. GAROFOLO[1], A. FATEMI[1,2], C. L. NEMETH[1,2];
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Abstract: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare white matter disease caused by mutations in the mitochondrial aspartyl-tRNA synthetase (mt-AspRS, or DARS2) gene, which is important for the synthesis of proteins in mitochondria. Abnormalities within cerebral white matter, brainstem, and spinal cord are observed in all patients, however, a large phenotypic spectrum exists. In an attempt to simulate an LBSL-like phenotype in mice, a Cre-lox recombination method was used to delete the Dars2 gene in specific cell types. Previously, we show that when Dars2 is deleted from CamkII alpha excitatory neurons, a severe and slowly progressive phenotype emerges beginning at 22 weeks consisting of significant cortical atrophy and ventricular enlargement (Nemeth et al., 2019). While useful for proof of concept studies and for therapeutic testing, these mice fail to show demyelination, a hallmark of LBSL. More recently, we have generated mice with Dars2 deletions in oligodendrocyte transcription factor 2 (Olig2) cells, early white matter cells that activate the expression of myelin-associated genes, and Advillin-expressing cells, or sensory neurons of the dorsal root ganglia. Mice are tested in multiple motor analyses, including gait assessments, Complex Wheel and Rotarod. Dars2/Olig2 knock-out mice show significantly reduced speeds and distance in the Complex Wheel ($p < 0.05$), compared to control mice, irrespective of the simple or complex wheel. Dars2/Advillin deletion mice display severe ataxic behavior starting at as young as p14, eventually leading to death by 8 weeks. In order to quantify the obvious impairments presented by these mice, gait analyses were performed at 4-6 weeks of age and histological assessments are underway. As LBSL patients primarily experience symptoms associated with ataxia and disordered gait, it is our hope that these models provide an accurate representation of disease phenotype for the further study of disease mechanism, cell-type specific effects, and therapeutic efficacy.

Disclosures: **I.L. Garofolo:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute. **A. Fatemi:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute,

Johns Hopkins University School of Medicine. **C.L. Nemeth:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute, Johns Hopkins University School of Medicine.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.02/D53

Topic: B.10. Demyelinating Disorders

Title: Hesperidin Improves Neurobehavioural Deficit in Cuprizone-induced Demyelination in swiss mice

Authors: *D. E. BABATUNDE[1,2], J. A. ADEDIJI[3], O. N. ADEYEMO[4], O. Y. OLAWEPO[4], P. G. AYUBA[4], S. F. LEWU[5], A. S. ALABI[6], O. OLABIYI[4], G. O. OMOTOSO[6]; [1]ANATOMY DEPARTMENT, ANATOMY PROGRAMME, COLLEGE OF HEALTH SCIENCES, BOWEN UNIVERSITY IWO, IWO, Nigeria; [2]Anat. department, FACULTY OF BASIC MEDICAL SCIENCES, UNIVERSITY OF ILORIN, ILORIN, NIGERIA, Ilorin, Nigeria; [3]Hlth. Information, Ctr. for Training Community Hlth. Officers, Univ. of Benin Teaching Hosp., Benin, Nigeria; [4]ANATOMY DEPARTMENT, Bowen Univ., Iwo, Nigeria; [5]ANATOMY DEPARTMENT, Univ. of Ilorin, Ilorin, Nigeria; [6]ANATOMY DEPARTMENT, Univ. of Ilorin, ILORIN, Nigeria

Abstract: Multiple sclerosis (MS) is one of the primary causes of neurological dysfunction, it is a chronic and complicated neuro-inflammatory demyelinating disease of the Central Nervous System (CNS). Hesperidin (HES), a bioflavonoid derived from citrus fruits, has been demonstrated through sufficient evidence to have inhibitory effects against neurodegenerative diseases. In this current study, we investigated the role of hesperidin in ameliorating the behavioral dysfunction and oxidative stress in the cuprizone (CPZ) induced demyelination model via provision of antioxidation. MS was induced in Swiss mice via combination of diet with CPZ (0.2%) for the first 3 weeks and HES (30mg/kg/day; IP) was administered for the last 2 weeks of treatment. Morris Water Maze Test (MWM) and open field test were performed as well as biochemical analysis including, malonaldehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and nitrite were all determined. HES treatment prevented body weight loss induced by CPZ. MWM test showed that CPZ increased the time spent in quadrant while in CPZ+HES group, the escape latency time increased. In the open field test, the result indicate that HES improve the ability to cross a greater number of lines, highest number of centre square entry and rearing frequency when compared to CPZ group which had reduced number of lines crossed, a smaller number of centre square entry and low rearing frequency. CPZ increased the level of MDA and GSH, reduced the level of SOD and CAT tested in the tissue homogenate of the corpus callosum of mice while HES alleviated this effect by providing antioxidant action thereby inhibiting oxidative stress. In conclusion, findings from the present study suggest that the beneficial properties of HES on CPZ induced demyelination are produced by inhibiting oxidative stress.

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Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.03/D54

Topic: B.10. Demyelinating Disorders

Title: Characterization of kynurenine pathway metabolites and proinflammatory profile in serum and cerebrospinal fluid of Mexican patients with Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory and demyelinating autoimmune disease that affects the Central Nervous System (CNS) with different clinical ways and phenotypes. In Mexico, around 20 thousand people suffer from MS, being the second cause of non-traumatic neurological disability in human productive ages. MS pathogenesis involves autoimmune processes triggered by environmental exposures, and mediated by T and B lymphocytes, and innate mechanisms in genetically predisposed individuals. Excitotoxicity is part of damage mechanisms, which has recently been associated with the kynurenine pathway (KP). KP increases tryptophan degradation in proinflammatory environments and leads to the production of metabolites with neuroactive, redox, and immunomodulatory properties as kynurenic acid (KYNA), 3 hydroxykynurenine (3-HK) and quinolinic acid (QUIN). For these reasons, the aim of this work was determining the levels of metabolites derived from tryptophan catabolism through the KP in serum and cerebrospinal fluid of "naive" Mexican patients with MS and patients with progressive MS (PMS). To achieve the objective serum and cerebrospinal fluid (CSF) samples from Mexican patients with naive MS (nMS) and PMS (with drug treatment), obtained between 2009 and 2016, were analysed for quantifying KP metabolites levels by HPLC and ELISA. The proinflammatory profile was evaluated by flow cytometry. For comparison, samples from patients with inflammatory neurological diseases (IND) were used. As results, no changes were found in the levels of KYNA with respect to healthy controls at peripherical level; while in CSF KYNA levels were similar to those found in subjects with IND. QUIN levels in the nMS and PMS groups were similar to the IND group in CSF, indicating an exacerbation of KP activity possibly due to the proinflammatory environment promoted by the presence of IL6 and TNF, which was also differential between nMS and PMS. TNF levels were

negatively correlated with CSF KYNA levels in nMS patients, while KYNA was negatively correlated with IL4 in PMS patients. The proinflammatory state in patients with naive MS and PMS promotes KYNA and QUIN production in the CNS, suggesting that these metabolites could be involved in the pathogenesis of MS and potentially be biomarkers of clinical progression in patients with MS.

Disclosures: P. Acosta Méndez: None. **T. Blanco Ayala:** None. **D. Ramírez Ortega:** None. **G. Perez de la Cruz:** None. **D.F. González Esquivel:** None. **B. Pineda:** None. **G. Ordoñez:** None. **J. Flores:** None. **V. Perez De La Cruz:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.04/D55

Topic: B.10. Demyelinating Disorders

Support: NRF-2021R1C1C2012889

Title: A novel zinc chelator reduces severity of experimental autoimmune encephalomyelitis in mice

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Abstract: Experimental autoimmune encephalomyelitis (EAE) is one of the most extensively used animal model in the development and testing of multiple sclerosis (MS) immune therapies and MS disease pathogenesis. Previously our lab described the pathogenic involvement of zinc deposition within the central nervous system (CNS) of EAE mice. In addition, we have demonstrated that 1H10, ameliorates experimental autoimmune encephalomyelitis by modulating zinc toxicity and AMPK activation. Recently we discovered a new derivatives compound with a structure similar to 1H10. This study aimed to evaluate the therapeutic efficacy of a novel zinc chelator (NZC) against myelin oligodendrocyte glycoprotein$_{35-55}$-induced EAE. Each group was subcutaneously injected NZC once per day for 60 days. We found that NZC profoundly reduced the clinical sign of EAE severity and that there was a remarkable decrease of demyelination, microglial activation and immune cell infiltration. Furthermore, NZC significantly suppressed MMP-9 activation, blood-brain barrier (BBB) damage, and abnormal synaptic zinc patch formation. Therefore, the present study suggest that NZC may have high therapeutic potential for the treatment of multiple sclerosis.

Disclosures: W. Yang: None. **J. Eom:** None. **Y. Kim:** None. **Y. Yoon:** None. **S. Suh:** None. **B. Choi:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.05/D56

Topic: B.10. Demyelinating Disorders

Support: BrightFocus Foundation (A2021025S)
Cure Alzheimer's Fund
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National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC)

Title: Meningeal lymphatic drainage regulates oligodendrocytes survival and brain myelination

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Abstract: Introduction The meningeal lymphatic vessels are constantly draining cerebrospinal fluid content to the cervical lymph nodes, and functional defects in this previously unappreciated brain lymphatic cleansing pathway have been linked to poor brain function. However, the impact of impaired meningeal lymphatic drainage on specific classes of brain molecules, namely on lipids is still unknown.The main purpose of this study is to explore if and how impaired meningeal lymphatic function can alter lipid composition and myelination in the brain.**Methods**Animals were injected with an adeno-associated virus (AAV) 9 encoding domains 1–3 of vascular endothelial growth factor receptor-3 (VEGFR3) coupled to an Ig domain, which traps circulating vascular endothelial growth factor (VEGF)-C and D, and leads to initial lymphatic vessel loss in the meninges. Control mice were injected with an AAV9 expressing the innocuous domains 4–7 of VEGFR3-Ig. Additionally, the cuprizone model was used to investigate the role of meningeal lymphatic loss during remyelination. The density of oligodendrocyte lineage cells was evaluated in mice with intact or ablated meningeal lymphatic vasculature at different time points post AAV9 injection and after different regimens of cuprizone.**Results**Decreased VEGF-C/D signaling resulted in altered myelin integrity, numbers of oligodendrocytes and oligodendrocyte gene expression. These results were recapitulated in a

genetic model of lymphatic endothelial cell loss. Importantly, the alterations in oligodendrocyte numbers were not recapitulated in models with an impaired immune system. Additionally, we observed that animals with impaired meningeal lymphatic function show a delay in the spontaneous remyelination process that occurs after cuprizone withdrawal.**Conclusion**Decreased meningeal lymphatic drainage is associated with marked changes in mature oligodendrocytes, brain demyelination, and delayed remyelination.

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Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.06/D57

Topic:

Support: CureLBSL
IDDRC NIH P50 HD103538

Title: Aav9 therapy for DARS2-related leukodystrophy, LBSL

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Abstract: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare neurological disorder caused by the mutations in *DARS2*, encoding the mitochondrial aspartyl-tRNA synthetase. LBSL has a wide phenotypic spectrum, characterized by childhood- or juvenile-onset slowly progressive spasticity, cerebellar ataxia and dysfunction of the dorsal column. Antenatal or infantile onset patients with profound cerebral hypoplasia and atrophy and early demise, as well as mild adulthood-onset patients, are also reported. Nearly all patients are compound heterozygous for *DARS2* mutations usually involving a missense and a frameshift mutation, leading to decreased abundance of the protein. To restore protein production within LBSL patient derived cells through the use of Adeno-Associated Viral (AAV) vectors, serotype 9, which target the CNS. *In vivo*, AAV vectors are capable of transducing human cells, have low toxicity, and persist over time without integrating into the genome. Motor neurons were derived from LBSL patient iPSCs according to an established protocol. On *in vitro* day 13,

neurons were treated with AAV9 vectors containing a DARS2 plasmid. Gene expression of *DARS2*, neuronal arborization, mitochondrial energetics, and lactate levels were measured during and after ten days of *DARS2*-AAV9 exposure. Results indicate increased of neuronal arborization, as well as increased expression of *DARS2* transcripts capable of protein production. Baseline mitochondrial respiration was increased however further testing is needed to understand effects to overall mitochondrial functioning. These results suggest that increasing normal *DARS2* production may reduce the phenotypic burden *in vitro*. Further testing is underway to understand the effects of AAV9 therapy on electrophysiological activity, long-term cell survival, and the effect of AAV9 in *in vivo* systems. Overall, gene therapies may work to slow or halt disease progression in those with LBSL.

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Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.07/D58

Topic: B.10. Demyelinating Disorders

Title: Development of an immunocompetent human brain organoid model of remyelination to assess safety and efficacy of drug candidates

Authors: *S. LANGE[1], J. HOEBER[1,2], S. KUSTERMANN[1];
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Abstract: Oligodendrocytes, the myelinating cells of the central nervous system (CNS) play a crucial role in axonal protection, structure and modulation of conduction. Protective myelin sheaths and eventually oligodendrocytes may be destroyed, due to inflammatory processes occurring in disease (eq. multiple sclerosis) or as an adverse drug-mediated side effect. Demyelination and myelin regeneration are mainly studied using rodent models. Due to species differences and experimental constraints, the translation from rodent findings into humans remains challenging. Human remyelination has rarely been studied in vitro due to the lack of comprehensive models encompassing all major CNS cell types.The development of a human immunocompetent brain organoid model to study de- and remyelination would allow to predict adverse side effects of novel drugs causing demyelination and/or neurotoxicity. This would facilitate safety assessments, while omitting interspecies differences. In parallel, this model could be used to perform efficacy assessments of drug candidates that promote remyelination in a human system. Our data suggest that our complex human CNS model can recapitulate the loss of myelin sheaths upon toxin-induced demyelination. These regenerate intrinsically, similar to the process of remyelination observed in tissue, and can be enhanced further by application of pro-

myelinating compounds.This immunocompetent human brain organoid model shows a high degree of physiological relevance for de- and remyelination. Thus, it presents a useful tool for safety and efficacy evaluation of drug candidates and to study human myelin biology more closely.

Disclosures: **S. Lange:** A. Employment/Salary (full or part-time):; Senior Scientist. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Roche employee; studies funded by Roche. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Data owned by Roche, Roche stock holder. **J. Hoeber:** A. Employment/Salary (full or part-time):; Senior Scientist. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Roche employee; studies funded by Roche. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Data owned by Roche, Roche stock holder. **S. Kustermann:** A. Employment/Salary (full or part-time):; Senior Principal Scientist. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Roche employee; studies funded by Roche. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Data owned by Roche, Roche stock holder.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.08

Topic: B.10. Demyelinating Disorders

Support: Sponsored Research Agreement-Autobahn Therapeutics

Title: Cortical myelin loss without optic nerve demyelination disrupts visual circuit function

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Abstract: Visual impairments are a common manifestation of demyelinating diseases such as multiple sclerosis (MS). While acute optic neuritis is a frequent and often initial symptom in MS, visual deficits occur even without a history of optic nerve inflammation indicating demyelination-induced damage in both the anterior and posterior visual pathways. Disruption to visual evoked potentials (VEP) latency is often used as supportive evidence to help confirm a

clinical diagnosis of multiple sclerosis as well as a biomarker for clinical trials. VEPs are a robust measurement in evaluating demyelination in animal models and recent work has confirmed that reduced VEP latency is driven by myelin regeneration. While VEP latency delays can be found in patients with MS with no history of optic neuritis, the contribution of demyelination in anterior and posterior visual pathways to visual deficits in patients with MS remains unclear. To explore the systems and circuit-level consequences of myelin loss on visual cortex function, we used acute treatment of 0.2% cuprizone (for 25 days) in 10-week-old *MOBP-EGFP* transgenic mice, which label all myelinating oligodendrocytes. This demyelinating injury resulted in functional changes in not only single-neuron response latency but also the ongoing temporal structure of VEPs. Next, we determined the dynamics and extent of oligodendrocyte loss in primary visual cortex (V1) using longitudinal *in vivo* two-photon imaging. We found that cuprizone-mediated demyelination resulted in a loss of 23.79±2.74% of the oligodendrocyte population. To examine the effects of acute cuprizone treatment on the anterior visual pathway, we used immunohistochemistry and confocal imaging of myelination and nodes of Ranvier in tissue collected from control and cuprizone-treated mice. In the optic nerve, we found no difference in the number of nodes of Ranvier (208.6±25.66 vs. 173.4±14.08 per 10000 μm^2) nor the mean gray values of PLP (52.05±7.34 vs. 49.51±4.75) between the cuprizone-treated mice and the control group. We also did not find differences in the number of oligodendrocytes in the optic tract (99.97±19.19 vs. 118.9±6.23 cells per $0.1mm^2$) or the dorsal lateral geniculate nucleus (176.4±16.01 vs.193.4±19.27 cells per $0.1mm^2$) between cuprizone-treated mice and the control groups. Thus, our results demonstrate that acute cuprizone treatment causes demyelination preferentially in the posterior part of the visual pathway, resulting in functional deficits. Together, our data suggest that demyelination in the posterior visual pathway can contribute significantly to visual latency delays.

Disclosures: A. Morris: None. **G. Dell Flora Nunes:** None. **E. Hughes:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.09/D59

Topic: B.10. Demyelinating Disorders

Title: Establishing the efficacy of thermoresponsive polymers in treating a murine model of experimental autoimmune encephalomyelitis

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Abstract: Experimental Autoimmune Encephalomyelitis (EAE) is the most commonly used experimental murine model for Multiple Sclerosis, a chronic autoimmune demyelinating disease in humans. We have previously demonstrated that delivery of glycolytic inhibitors and metabolites such as alpha-ketoglutaric acid in a sustained fashion can lead to generation of

immunosuppressive T cells. We have also demonstrated that these immunosuppressive T cells can reach the site of inflammation and reduce inflammation. In this study, we used thermoresponsive polymer that is liquid at 4° but gel at room temperature, to deliver peptides that are helpful in stimulating an immunosupressive response. Specifically, Hooke's Emulsion kits with the peptide MOG, Complete Freund's Adjuvant, and Pertussis toxin were used for disease induction in C57BL/6 mice. The first group of 15 mice was treated once with the peptides (I.P.) on day 6 followed by GFP-sorted regulatory T cells (R.O.) on day 7. These 15 mice were sacrificed on day 14. Immune responses were determined in the brain, spleen and lymph nodes using flow cytometry. The second group of 30 mice was used for the survival study. These mice were treated with peptides twice on days 6 and 11 as well as with GFP-sorted regulatory T cells on days 7 and 12. All mice were scored on a scale of 0-5 based on EAE symptoms and weighed at regular intervals to monitor disease progression. It was determined that indeed our formulation was able to generate MOG-specific regulatory T cells and Th2 cells in the brain and generate alternatively activated macrophages in the spleen. Moreover, as compared to no treatment control, our formulation was able to delay the onset of the disease in these mice. Overall, the data here suggests that the formulations generated can be used for treatment for EAE in mice, and potentially provide one time treatment for MS in humans.

Disclosures: S.J. Swaminathan: None. **M.M.C.S. Jaggarapu:** None. **A.P. Acharya:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.10/D60

Topic: B.10. Demyelinating Disorders

Support: NIMH Grant R33MH104330

Title: Anesthetics and Myelin Decompaction in Adult Mice

Authors: *C. BEST, R. KNICKMEYER, H. DUBEY, S. LIU, A. WHITE;
Inst. for Quantitative Hlth. and Engin., Michigan State Univ., East Lansing, MI

Abstract: Myelination is an important neurodevelopmental process in which oligodendrocytes surround axons with an insulating sheath, thereby increasing the speed of neural signals. Previous studies show that the presence of anesthetics such as isoflurane during critical periods of mouse development hinder neuronal and oligodendrocyte development, altering myelination and overall brain function. However, these studies have only examined the impact of anesthetics on very young mice, and while they have examined anesthetics' effects on myelin sheath thickness, they have not explored the impact of anesthetics on myelin sheath decompaction. As part of a study on the microbiome-gut-brain axis, myelin phenotypes for 28 adult mice (16 male, 12 female) were assessed using electron microscopy. 18 of these mice (10 male, 8 female) underwent MRI scanning prior to sacrifice, and were administered isoflurane and

Dexmedetomidine. Axons in the prefrontal cortex, amygdala, nucleus accumbens, and hippocampus were assessed for myelin decompaction level, axonal diameter, myelin sheath thickness, and number of myelin lamina using ImageJ software. Myelin decompaction level was measured by three separate individuals to confirm reliability. Preliminary results show that anesthetic protocol may impact myelin decompaction level, as mice that received anesthetics, on average, had around 1.6 times the proportion of highly decompacted axons that anesthetic-free mice had. This difference was significant with a p-value of 0.01. Mice that received anesthetics also had, on average, axons with significantly lower numbers of individual myelin sheath layers than those who were anesthetic-free; this difference was significant with a p-value of 0.0003. Interestingly, axonal diameter and myelin sheath thickness were not impacted by anesthetic status. Gut microbiome composition and sex do not appear to play a significant role in decompaction or myelin sheath layers. To our knowledge, this is the first study showing that this particular anesthetic protocol may induce demyelination and myelin decompaction in adult animals. If confirmed in future studies, this information has the potential to change the field of anesthesia, both in animal and human care.

Disclosures: **C. Best:** A. Employment/Salary (full or part-time):; Michigan State University. **R. Knickmeyer:** A. Employment/Salary (full or part-time):; Michigan State 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.; Michigan State University. **H. Dubey:** A. Employment/Salary (full or part-time):; Michigan State University. **S. Liu:** A. Employment/Salary (full or part-time):; Michigan State University. **A. White:** A. Employment/Salary (full or part-time):; Michigan State University.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.11/D61

Topic: B.10. Demyelinating Disorders

Support: R01NS107523

Title: Investigating the Role of the T Cell Amino Acid Transporter Slc7a5 in a Mouse Model of Multiple Sclerosis

Authors: *M. COZART, M. BAYDYUK, J. HU, Z. MANAVI, J. HUANG;
Georgetown Univ., Washington, DC

Abstract: Multiple Sclerosis (MS) is an immune-mediated disease characterized by the infiltration of T cells into the central nervous system (CNS), contributing to inflammation and demyelination. Chronic demyelination leads to axonal damage and progressive neurodegeneration. The large amino acid transporter 1 (LAT1), also known as *Slc7a5*, is known

to control T cell metabolism and differentiation. However, whether Slc7a5 plays a role in T-cell-associated pathology in MS is unknown. Here, to examine CD4 T cell-specific *Slc7a5* loss of function in immune-mediated demyelination, we generated a CD4-Cre; *Slc7a5*$^{f/f}$ (cKO) mouse line. Preliminary data show that these mice do not develop clinical disability after myelin oligodendrocyte protein (MOG) mediated experimental autoimmune encephalomyelitis (EAE) induction compared to control mice. Flow cytometry analysis of the spleen, spinal cord, and lymph nodes from cKO mice revealed differentiation of CD4+ T cell populations in the spleen and lymph nodes, but a significant decrease of these cells in the spinal cord compared to the control. Our results suggest *Slc7a5* in CD4+ T cells is necessary to establish CNS inflammation, and *Slc7a5* is a potential novel immunomodulatory target for reducing or preventing inflammation in the CNS during demyelination in MS.

Disclosures: **M. Cozart:** None. **M. Baydyuk:** None. **J. Hu:** None. **Z. Manavi:** None. **J. Huang:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.12/D62

Topic: B.10. Demyelinating Disorders

Support: Health and Medical Research Fund, Health Bureau, HKSAR Government (05163296 & 06173706)

Title: Towards use of bone marrow stromal cell-derived fate-committed glial precursors for remyelination therapy

Authors: *K.-W. TAM[1], C.-Y. WONG[1], X. LIANG[1], Y.-S. KEUNG[1], W.-P. WONG[1], W.-Y. LI[1], W.-T. WONG[1], M.-S. LI[1], Y.-P. TSUI[1], G.-H. SHEA[2], D.-Y. SHUM[3], Y.-S. CHAN[3]; [1]Sch. of Biomed. Sci., [2]Dept. of Orthopaedics and Traumatology, [3]Sch. of Biomed. Sci. & State Key Lab. of Brain and Cognitive Sci., The Univ. of Hong Kong, Hong Kong, China

Abstract: Donor nerve-derived Schwann cells transplanted to the severed nerve/tract in the PNS/CNS improves prospects of post-traumatic recovery in rat models. Clinical translation however requires sufficient quantities of immuno-compatible and fate-committed glial precursors. To this end, we enriched the neuroprogenitor subpopulation among human bone marrow (hBM) stromal cells in culture and then with selected glia-inducing supplements, yielded either Schwann cell-like cells (SCLCs) or oligodendrocyte precursors (OPs). Coculture with hiPSC-derived neurons committed SCLCs to the SC fate and OPs to the oligodendroglial fate. The derived hSC and OPs were cryopreserved and thawed on demand for tests in rat models of (1) sciatic nerve injury, (2) thoracic cord injury and (3) experimental autoimmune encephalomyelitis (EAE). By 12-week post-treatment, significant improvement in hindlimb motor function, evoked signals on the treated side and axons myelinated by hBM-derived SCs

were evident in (1). Similar results were not observed in (2) unless treatment with hBM-derived SCs was paired with chondroitinase ABC to address the glial scar. With hBM-derived OPs, by 5-week post-treatment in (3), the daily average EAE scores of the treated group were lower than those of the vehicle control group. Results provide the evidence that supports use of marrow stromal cell-derived myelinating cells in autologous cell-based transplantation for remyelination therapy.
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Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.13/D63

Topic: C.06. Neuromuscular Diseases

Support: PHS NCCR # TL1RR025759
PHS NCCR # RR025761

Title: Up and down Regulation of Aldehyde Expression by External and Internal Mechanisms and their Therapeutic Value in EAE Mice

Authors: *A. ALFORD[1,2], J. TANG[2,3,1], G. LEUNG[2,3], M. TULLY[1,4,2], R. SHI[3,1,2];
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Abstract: Acrolein, a pro-inflammatory aldehyde, has been shown to be a critical factor in MS pathology. It has been demonstrated that the acrolein scavenger hydralazine (HZ) can suppress acrolein as well as alleviate motor deficits in a mouse model of MS, experimental autoimmune encephalomyelitis (EAE). We therefore hypothesize that the up and down regulation of aldehyde dehydrogenase 2 (ALDH2), an enzyme capable of metabolizing aldehydes, could instigate behavioral changes in EAE. With the use of three structurally distinct acrolein scavengers, we have shown that acrolein scavengers are capable of mitigating motor and sensory deficits in EAE when applied post-induction. Particularly, HZ was found capable of alleviating motor deficits when application was delayed until symptom emergence. This additionally corresponded to a reduction in both acrolein and inflammatory markers in EAE mice. Furthermore, through a genetically modified mouse model, we can emulate a clinically relevant ALDH2 deficiency that is prevalent in East Asian populations. We have found that these ALDH2*2 mice not only display more severe behavioral deficits, but also heightened levels of acrolein, inflammation, and

demyelination markers in EAE compared to wild-type mice. In addition, treatment with Alda-1, an activator of ALDH2, can lower acrolein and inflammation in EAE, which is associated with reduced motor impairments and sensory hypersensitivity. These findings further consolidate the critical role of aldehydes in the pathology of EAE and its mechanisms of regulation. This is expected to reinforce and expand the possible therapeutic targets of anti-aldehyde treatment to achieve neuroprotection through both endogenous and exogenous manners.

Disclosures: **A. Alford:** None. **J. Tang:** None. **G. Leung:** None. **M. Tully:** None. **R. Shi:** A. Employment/Salary (full or part-time):; Co-founder of Neuro Vigor, a start-up company with business interests of developing effective therapies for CNS neurodegenerative diseases and trauma.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.14/D64

Topic: C.06. Neuromuscular Diseases

Support: US Department of Veterans Affairs BX004209
NIAID AI22574
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NIAID AI148409

Title: PD-L1 is required for estrogen-induced protection against severe EAE in IL-10 deficient mice

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Abstract: Interleukin 10 (IL-10) knockout (KO) mice can be protected against experimental autoimmune encephalomyelitis (EAE) with low-dose estrogen (E2) treatment similar to wild type (WT) mice, indicating that IL-10 is not required for E2-induced EAE protection. Our previous study demonstrated that E2 treatment induced an increase in programmed death ligands 1 (PD-L1) and 2 (PD-L2) on monocytes and macrophages in the periphery and within the CNS. In this study, we selectively inhibited the function of PD-L1 and PD-L2 to evaluate their critical role in maintaining E2-induced protection against EAE in IL-10-KO mice. This study used female IL-10 KO mice pre-treated with either E2 or sham pellets seven days prior to induction of EAE and subsequently treated with Vehicle or antibodies to PD-L1, PD-L2 or respective isotype controls. Mice were scored daily for EAE severity over 21 days post-EAE induction. Cells from the spleen and brain were evaluated by flow cytometry. Differences in EAE severity were

assessed in E2 and sham pre-treated IL-10-KO mice treated with α-PD-L1 or α-PD-L2 antibodies over the course of disease compared to treatment with Vehicle or isotype control antibodies. The results revealed real-time development of severe EAE in E2-pre-treated IL-10-KO mice treated with α-PD-L1 but not α-PD-L2 antibodies, mediated in part by increased percentages of activated CD74+CD11b+ myeloid cells in spleen and brain as well as splenic B-cells, T-cells and CD73+ cells. These results demonstrate unequivocally that PD-L1 but not PD-L2 was required to retain the inhibitory effects of E2 on clinical EAE scores in female IL-10-KO mice and further implicate the emergence of the MIF/CD74 axis as a contributing pathogenic mechanism.

Disclosures: H. Offner: None. **D.R. Lockwood:** None. **R. Meza-Romero:** None. **A.A. Vandenbark:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.15/D65

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grant-in-Aid for a Kitasato University School of Allied Health Sciences Research Project 2018-1005
Grant-in-Aid for a Kitasato University School of Allied Health Sciences Research Project 2019-1005
JSPS KAKENHI 17K08604
JSPS KAKENHI 21K06603

Title: Genetic deletion of microsomal prostaglandin E synthase-1 suppresses cuprizone-induced demyelination and motor dysfunction in mice

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Abstract: Multiple sclerosis (MS) is one of the most common demyelinating diseases. Microsomal prostaglandin E synthase-1 (mPGES-1) is a key enzyme that acts downstream of cyclooxygenase (COX) and plays a major role in inflammation and immune responses by converting prostaglandin (PG) H_2 to PGE_2. PGE_2 is highly produced in the cerebrospinal fluid of patients with MS. However, the role of mPGES-1 in MS has not been fully elucidated yet. In this study, we demonstrate the role of mPGES-1 in demyelination and motor dysfunction induced by cuprizone, one of the well established models of MS. Demyelination in the brain was induced in

mice lacking mPGES-1 (mPGES-1$^{-/-}$ mice) and wild-type (WT) mice by feeding ad libitum with a powdered diet containing 0.2% cuprizone for 6 weeks under specific pathogen free condition. The expression of mPGES-1 and COX-2 in the brain was determined by real-time PCR. The cuprizone-induced demyelination was assessed by a myelin staining with coronal brain sections, and motor dysfunction was evaluated by the rotarod test. In the brain of WT mice, the expression of mPGES-1 mRNA was basally detectable and increased at 6 weeks after the start of cuprizone administration. As expected, mPGES-1 expression was completely abolished in mPGES-1$^{-/-}$ mice either with or without cuprizone administration. COX-2 mRNA was also expressed in the brain, but the expression level was similar in both mPGES-1$^{-/-}$ and WT mice. After cuprizone administration, the level of brain PGE_2 in mPGES-1$^{-/-}$ mice was significantly lower than in WT mice. Notably, even in normal brain without cuprizone, mPGES-1 genetic deletion resulted in greater reduction of brain PGE_2 when compared to WT mice. These data clearly indicate that mPGES-1 is the main synthase responsible for brain PGE_2 production not only in abnormal condition but also in the healthy condition. Histological analysis by a myelin staining with coronal brain sections further showed that WT mice developed severe demyelination after administration of cuprizone. Interestingly, mPGES-1$^{-/-}$ mice exhibited lower degree of demyelination compared to WT mice. In addition, mPGES-1 genetic deletion suppressed cuprizone-induced motor dysfunction. Furthermore, COX-2 selective inhibitor celecoxib also reduced cuprizone-induced motor dysfunction in association with inhibition of PGE_2 production in the brain. These data suggest that COX-2/mPGES-1/PGE_2 system might contribute to the pathophysiology of MS. Our findings provide novel insights relevant to the therapeutic potential for pharmacologic inhibition of mPGES-1 in demyelinating diseases including MS.

Disclosures: **Y. Hioki:** None. **F. Kojima:** None. **R. Mutaguchi:** None. **K. Eto:** None. **M. Ogata:** None. **S. Sasaki-Hamada:** None. **T. Ichikawa:** None. **H. Ishibashi:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.16/D66

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Uncover the mechanism of demyelinating diseases with single-cell spatial multi-omics

Authors: *Y. WANG[1], A. WANG[2];
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Abstract: Demyelinating diseases, including conditions like multiple sclerosis, acute disseminated encephalomyelitis, and Baló's disease, affect over a million people. Yet, the exact processes that cause myelin damage in these diseases largely remain elusive. In this study, we examine the brain sections of demyelinating mice (female, 2 months old) using cutting-edge single-cell spatial transcriptomics technologies like CosMx, Stereo-seq, Xenium, Visium,

GeoMx, along with advanced epigenetic and metabolomics tools such as sc-spatial ATAC and imaging mass spectrometry, to unravel the roles of several signaling pathways in the development of these diseases, like cell cycle arrest at G2 phase, dysregulated lipid metabolism, and vesicle transport. Integration of the data with supervised machine learning offers a panoramic view to deepen our understanding of these diseases.

Disclosures: Y. Wang: None. **A. Wang:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.17/D67

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ministry of Science and Technology of China 2020YFC2002800
Ministry of Science and Technology of China 2021ZD0200900
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Innovative Research Team of High-Level Local Universities in Shanghai

Title: Intestinal DRD2 regulates sex-dimorphism in multiple sclerosis animal model

Authors: *Y. ZHANG[1], H. PENG[2], J. ZHOU[3];
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Abstract: Sex dimorphism is implicated in multiple neurological diseases in terms of disease susceptibility, pathology, and progression. The contributions of sex hormones, genetic and epigenetic difference, gut microbiota alterations have been linked to the development of sexual preference during central nervous system (CNS) autoimmune diseases. Among them, multiple sclerosis (MS) is known for its much higher risk with female individuals. Studies to date have investigated the relevance of pregnancy, hormonal factors, and sex-specific epigenetic changes, but we still lack knowledge of the sex-related difference dependent of gut-brain axis in MS.

Here, we show that intestinal epithelial dopamine D2 receptors (iDRD2) promote disease progression in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, through the action of intestine-originated lysozyme exclusively in female mice. We find that in female mice genetically abolished of iDRD2, but not male mice, inflammatory responses and neurodegeneration are greatly inhibited upon EAE challenge. In contrast, activation of iDRD2 through pharmaceutical or genetic approach could exacerbate CNS inflammation and disease severity only in female animals. Based on RNA-seq data of intestinal epithelium and 16S rRNA sequencing of fecal microbiota, we identify Paneth cells derived lysozyme, a bactericidal polypeptide, and lysozyme-sensitive *Lactobacillus* as regulators downstream of iDRD2 manipulation. To further investigate the linkage of gut-brain axis in our animal model, we perform untargeted metabolites profiling of the spinal cord tissue and find significantly altered level of N2-acetyl-L-lysine (NAL) in female iDRD2 knock-out mice with alleviated EAE symptoms. Furthermore, we observe that administration of NAL ameliorates EAE progression, as well as microglia activity, only in female mice in a dosage-dependent manner. We then evaluate the transcriptomic profile of isolated microglia during the peak of EAE using magnetic-activated cell sorting and RNA-seq analysis. Marked reduction of sphingosine kinase 1 (Sphk1) mRNA expression and deregulated sphingosine metabolism pathway are hinted in the results. Finally, we confirm the impact of NAL on microglial Sphk1 expression *in vivo*and *in vitro* with microglial BV2 cell lines. To sum up, we uncover a novel role of iDRD2 in regulating sex-biased disease progressing in MS animal model.

Disclosures: **Y. Zhang:** None. **H. Peng:** None. **J. Zhou:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.18/D68

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Jaschafonden
The Multiple Sclerosis Society
Oda og Hans Svenningsens Fond
Inger Bonnens Fond
Dagmar Marchalls Fond
Minister Erna Hamiltons Fond

Title: Unraveling the Protective Potential MIF against Brain Damage in Multiple Sclerosis

Authors: *A. FEX SVENNINGSEN, S. HJÆRESEN;
Univ. of Southern Denmark, Odense, Denmark

Abstract: Multiple Sclerosis (MS) is a complex autoimmune disease characterized by inflammation and demyelination in the central nervous system. Macrophage Migration Inhibitory

Factor (MIF) is a cytokine implicated in various inflammatory conditions, including MS. Our previous findings revealed a paradoxical decrease in MIF levels during relapsing remitting MS (RRMS) followed by an increase during secondary progressive MS (SPMS). This intriguing observation prompted us to explore the expression and functional role of MIF in a mouse model of MS, specifically the cuprizone model, as well as *in vitro* experiments. Utilizing the cuprizone model, we observed that MIF was predominantly expressed in neurons of the cortex and, during the degeneration and regeneration phases of cuprizone treatment, in astrocytes and oligodendrocyte precursors (OPCs). Furthermore, we found that MIF expression decreased during both degeneration and regeneration in this model. *In vitro* experiments demonstrated that a decrease in MIF levels resulted in suppressed glial cell proliferation and microglia phagocytosis. The absence of MIF also hindered the motility of OPCs and neural outgrowth.The reduction in MIF expression observed in the cuprizone model aligns with our previous findings in RRMS patients. This decrease in MIF levels may represent a protective response to mitigate brain inflammation, as it diminishes the proliferation of astrocytes and microglia. This protective mechanism comes at a cost, as it also impedes OPC proliferation, motility, and neural outgrowth. The research sheds light on the dynamic role of MIF in the pathogenesis of MS and highlights the complex interplay between MIF and the cells of the CNS.

- Our findings indicate a consistent decrease in MIF expression in both RRMS patients and the cuprizone model.
- Decreased MIF levels negatively impact the proliferation of all glial subtypes.
- Diminished MIF expression compromises the proliferation and migration of OPCs, as well as neural sprouting.
- The decrease in MIF levels may serve as a protective response to mitigate brain inflammation by reducing the proliferation of astrocytes and microglia.
- This protective mechanism also hampers OPC proliferation, motility, and neural outgrowth.

Disclosures: **A. Fex Svenningsen:** None. **S. Hjæresen:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.19/D69

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Marie Jönsson
Jascha Fonden
Scleroseforeningen
Oda og Hans Svenningsens Fond

Købmand Inger Bonnens Fond
Th. Maigaards eftf. Fru Lily Benthine Lunds Fond af 1.6.1978

Title: Htra1: an intriguing player in multiple sclerosis pathogenesis, shaping inflammation, myelination, and neural outgrowth

Authors: *S. HJÆRESEN[1], A. FEX SVENNINGSEN[2];
[1]Univ. of Southern Denmark, Odense C, Denmark; [2]Univ. of Southern Denmark, Univ. of Southern Denmark, Odense, Denmark

Abstract: Background: Multiple sclerosis (MS) is a neuroinflammatory disease characterized by demyelination in the central nervous system. High Temperature Requirement protein A1 (HTRA1) has emerged as a potential player in MS pathogenesis, with its levels increasing in cerebrospinal fluid during disease progression. Notably, immunomodulatory treatment reduces HTRA1 levels, suggesting its involvement in the immune response. To unravel the expression and function of HTRA1, we employed HTRA1 overexpressing mice (HTRA1 tg) and conducted cell culture experiments. **Results:** HTRA1 was found to be expressed in astrocytes and blood vessels within the mouse brain. Adult HTRA1 tg mice exhibited a smaller corpus callosum, accompanied by a decrease in the population of oligodendrocyte precursors (OPCs). *In vitro* experiments demonstrated that HTRA1 reduced the number of OPCs while increasing astrocytes, and in combination with INFγ HTRA1 enhanced OPC migration. HTRA1 was shown to impair neural outgrowth. **Discussion:** Our findings shed light on the multifaceted role of HTRA1 in MS pathogenesis, implicating its involvement in myelination, and neural development. The observed increase in HTRA1 levels during disease progression suggests a potential role in promoting inflammation. However, the relationship between HTRA1 and the immune system remains unclear, as contradictory effects on astrocyte proliferation and other cell types have been reported. Importantly, elevated HTRA1 levels were found to hinder OPC proliferation thus compromising the remyelination processes, while also impairing neural outgrowth. **Conclusions:** The increase in HTRA1 levels during MS progression suggests a potential role in promoting inflammation in the central nervous system. Overexpression of HTRA1 leads to structural alterations, including a smaller corpus callosum, emphasizing its influence on brain morphology. HTRA1 negatively affects OPC population, which may contribute to impaired remyelination in MS. Elevated HTRA1 levels hinder neural outgrowth, indicating a broader impact on neuronal development.

Disclosures: S. Hjæresen: None. **A. Fex Svenningsen:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.20/D70

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Penn State Behrend
Hamot Health Foundation

Title: Oligodendrocyte derived extracellular vesicle release is altered by endoplasmic reticulum stress

Authors: E. EVALT, S. GOVINDARAJ, M. JONES, N. OZSOY, *A. RUSSELL;
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Abstract: Oligodendrocytes, an important glial cell of the CNS, form myelin sheaths around neuronal axons necessary for insulation and facilitating electrical signaling. These sheaths are composed of proteins and lipids which are synthesized, folded, and transported by the endoplasmic reticulum (ER) of the cell. Disruptions to ER protein synthesis can cause ER stress, leading to the activation of the unfolded protein response. Since oligodendrocytes heavily rely on protein production, they are particularly vulnerable to the harmful effects of ER stress. Previous studies have shown that ER stress can alter the release and composition of extracellular vesicles (EVs) in some cell types, but the effects on oligodendrocytes have not previously been reported. EVs are tiny (50-500 nm) lipid-membrane structures released from all cells and found in all biological fluids, including conditioned cell culture media (CCM), and contain bioactive proteins, lipids, and nucleic acids. This study aims to determine the effects of ER stress on oligodendrocyte EV release and composition. To induce ER stress, human oligodendroglioma (HOG) cells were treated with tunicamycin. Cell death and viability assays (LDH and CCK8, respectively) were performed to determine the optimal concentration of tunicamycin for downstream experiments, which was found to be 10 ug/mL. To confirm successful induction of ER stress, western blotting was performed and significant upregulation of ATF6, RL90/PDI, and BIP were observed in tunicamycin treated cells, relative to control. Further, we observed significant upregulation of the autophagy related proteins Beclin 1, LC3a, and LC3b in tunicamycin treated cells, indicating activation of both ER stress and autophagy pathways. Next, we used size exclusion chromatography (SEC) to separate EVs and small extracellular proteins from the conditioned CCM of tunicamycin treated and control cells after a 24-hour exposure period. Through western blotting, we confirmed successful separation of EVs by observing the canonical EV markers CD63, CD9, and CD81 in the EV fraction, and their absence in the protein fraction. Further, transmission electron microscopy was used to visualize the samples, and EVs with the expected cup-like morphology were observed in the EV fractions, with no EVs in the protein fractions. Together, these data suggest that ER stress activates autophagy related paathways and increases EV release from HOG cells. We are now working to determine how ER stress may modulate EV cargo by assessing protein and microRNA profiles, and how these EVs may impact the functionality of naïve cells exposed to them.

Disclosures: E. Evalt: None. **S. Govindaraj:** None. **M. Jones:** None. **N. Ozsoy:** None. **A. Russell:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.21/E1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Ginsenoside-Re inhibits experimental autoimmune encephalomyelitis as a mouse model of multiple sclerosis by downregulating TLR4/MyD88/NF-κB signaling pathways

Authors: *I. CHO[1], J. OH[2], J. CHOI[2], T. KWON[2];
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Abstract: Background: Ginsenosides are main active compounds of *Panax ginseng* with pharmacological effects on immunological/neurological diseases. Recently, ginsenoside-Re (G-Re) has been shown to exert neuroprotective effects on neurodegenerative diseases such as Alzheimer's disease. However, the effect of G-Re on multiple sclerosis (MS), a representative autoimmune disease of central nervous system (CNS), has not been revealed yet. **Purpose and Methods:** Here, we investigated the pharmacological effects and molecular mechanisms of G-Re in a myelin oligodendrocyte glycoprotein peptide-immunized experimental autoimmune encephalomyelitis (EAE), an animal model of MS, and lipopolysaccharide (LPS)-stimulated bEND.3 cells, an *in vitro* model of the blood-brain barrier (BBB). **Results:** G-Re attenuated motor impairment of EAE, demyelination, and inflammation in spinal cords of EAE mice. G-Re reduced infiltration/activation of microglia/macrophages and decreased mRNA expression levels of pro-inflammatory cytokines (IL-1β and IL-6), chemokines (MIP-1α, MCP-1, and RANTES), and enzymes (COX-2 and iNOS) in spinal cords of EAE mice. G-Re inhibited alterations of BBB constituents such as astrocytes, cell adhesion molecule (platelet endothelial cell adhesion molecule-1), and tight junctional molecules (occludin and zonula occludens-1) as well as toll like receptor 4 (TLR4)/MyD88/nuclear factor kappa-B (NF-κB) signaling pathways in spinal cords of EAE mice and LPS-stimulated bEND.3 cells. **Conclusions:** G-Re might alleviate motor impairment of EAE and its pathological/inflammatory events in the spinal cord by preventing BBB disruption via downregulation of TLR4/MyD88/NF-κB signaling pathways. These findings suggest that G-Re might be a potential therapeutic for MS through maintenance of BBB integrity.

Disclosures: I. Cho: None. **J. Oh:** None. **J. Choi:** None. **T. Kwon:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.22/E2

Topic: C.06. Neuromuscular Diseases

Title: Multiple Sclerosis Gait Rehabilitation with a Brain-Computer Interface System

Authors: *C. GUGER[1], K. MAYR[1], M. SEBASTIÁN-ROMAGOSA[2];
[1]g.tec medical engineering GmbH, Schiedlberg, Austria; [2]g.tec medical engineering Spain SL, Barcelona, Spain

Abstract: Multiple sclerosis (MS) is a chronic neurodegenerative disease in which a person's immune system attacks healthy nerves. People with MS (PwMS) often experience pain, fatigue, cognitive dysfunction, and reduced mobility. Great efforts have been made to understand the basis of MS and to provide new treatments, including medications, implanted and external devices, dietary and lifestyle changes, and therapy. However, MS is incurable and treatments can, at best, slow the progression of the disease and manage some symptoms. In this study, an EEG-MI-based BCI system is used to train the functionality of pwMS by reducing fatigue and improving gait ability and endurance. Seven MS patients were enrolled in this study. All completed 30 recoveriX sessions (15 sessions with the left-hand vs. right-foot paradigm and 15 sessions with the right-hand vs. left-foot paradigm). The results show that walking endurance improved from 198 m IQR = [115.34 to 205.06] (baseline) to 213.7 m IQR = [150.8 to 273.5] (post-assessment). The median difference was 61.88 m IQR = [10.7 to 65.69], Z = 2.42, P = 0.031. After treatment, patients reported an improvement in their physical and psychological functioning. This improvement can be explained by the results on the MSIS29, -10 points IQR = [-12.5 to -9], Z = 6.686, P = 0.003. These changes correlate with the reduction in fatigue as assessed by the MFIS test. Patients reduced their fatigue by a mean of -6.5 points IQR = [-11.5 to -2.75], Z = 2.247, P = 0.078. This is the first study that analyzes the effectiveness of BCI-based treatment in pwMS. BCI therapy may be good training for gait rehabilitation in patients with multiple sclerosis by reducing fatigue, increasing safety, and optimizing treatment time.

Disclosures: **C. Guger:** A. Employment/Salary (full or part-time):; Full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Director of the company. **K. Mayr:** A. Employment/Salary (full or part-time):; Full. **M. Sebastián-Romagosa:** A. Employment/Salary (full or part-time):; Full.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.23/E3

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Undergraduate Research Opportunities Program

Title: Development of a novel model of myelin degeneration in adult Drosophila melanogaster

Authors: M. ZINKEVITCH, K. OJEDA, A. WOODARD, ***P. HARVEY**;
Univ. of Colorado Boulder, Boulder, CO

Abstract: Despite decades of research on lipid homeostasis and its relationship to heart health, the role of lipids in the development and progression of neurological diseases has not been

thoroughly explored. Patients with neurodegenerative diseases, including multiple sclerosis (MS), often present with dyslipidemia. A small number of nutritional studies dating back to the 1980's and a recent study in mice suggest that dietary manipulation of serum cholesterol concentrations can dramatically affect the degree of myelination in the brain and progression of neurodegenerative diseases like MS. Despite empirical and anecdotal evidence, little consideration has been given to the link between the liver's ability to regulate serum lipids and brain health.
Currently, animal models of MS involve viral infection or chemical toxin-mediated demyelination, which are not accepted causes of MS in patients. An inflammatory component is common to both models and patients. However, the cause and significance to the disease is unknown. We hypothesize that elevated systemic cholesterol may play a role in the rate of central nervous system demyelination that occurs in MS. To test this, we use Drosophila melanogaster, an established model in the study of neurodegenerative diseases and cholesterol homeostasis disorders. More than 90 cytochrome p450 genes, including those involved in metabolizing lipids and cholesterol in the mammalian liver, are encoded in the fly genome. Consideration of cholesterol in neurological disease provides an opportunity to identify mechanisms of disease progression that have otherwise been overlooked in mammals.
To accurately represent adult-onset disease, we use double-stranded RNA (dsRNA) injections in adult Drosophila melanogaster to allow for normal organismal development. dsRNA-mediated knockdown has yielded genetic information critical to our understanding of development and gene function. Previous studies, however, have been limited to embryonic stages due to challenges associated with injecting dsRNA in the adult. Here, we report an expression analysis of 19 genes involved in dsRNA cellular uptake and processing at time points taken at 12-hour intervals from 0-7 days after eclosure. These data provide a valuable resource for optimizing conditions for dsRNA injection and successful gene silencing in adult Drosophila melanogaster. We hypothesize that disruption of lipid homeostasis through gene knockdown will produce phenotypes in human disease and that our approach will represent a novel way to examine the causal mechanisms of demyelinating diseases.

Disclosures: **M. Zinkevitch:** None. **K. Ojeda:** None. **A. Woodard:** None. **P. Harvey:** None.

Poster

PSTR071. Multiple Sclerosis, Leukodystrophies, and Mechanisms of Myelination

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.24/E4

Topic: B.10. Demyelinating Disorders

Support: Multiple Sclerosis Society of Great Britain 109

Title: Genome-wide screening of gene variants influencing the clinical course and pathological severity of multiple sclerosis

Authors: *I. FARKAS[1], Y.-Y. LEUNG[1], B. COOZE[3], M. AFONSO MOTA CRUZ PEREIRA[1], D. GVERIC[1], R. NICHOLAS[1], O. HOWELL[3], P. SRIVASTAVA[2], D. OWEN[1], R. REYNOLDS[1];
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Abstract: Identification of genetic variants that contribute to the heterogeneity of clinical disease in multiple sclerosis (MS) is critical to our understanding of disease mechanisms and development of appropriate therapeutics for progression. However, studies that explore the relationship between genetic factors, clinical outcome and pathological measures are currently limited. We have used natural language processing aided analysis of clinical histories, high throughput image feature extraction for quantitative neuropathological measures and genome-wide association (GWAS) single nucleotide polymorphism (SNP) analysis on a cohort of 315 post-mortem MS brains (MS Tissue Bank, Imperial College). Neuron density (HuC+ cells/mm^2) was assessed by immunohistochemical staining of tissue from 6 brain regions of the same MS cohort. The associations of clinical and neuropathological features were evaluated with an ensemble of GWAS statistics that integrated SNP, gene and gene-set level associations, as well as expression quantitative trait loci (eQTLs), single cell RNAseq and bulk tissue transcriptomics data. Following quality control, SNP level associations were integrated with functional information from eQTLs of 18 nervous and immune tissues in the GTEX database and with the quantitative data on neuron numbers. Using Bayesian Test for Colocalization (COLOC) statistics, we identified 331 candidate hit genes with >50% posterior probability that the GWAS and eQTL traits shared a causal variant associated with clinical outcome and 360 associated with neuron number. Combining information of enriched biological processes in the COLOC hit genes suggests that pathways related to cell death, lipid metabolism and vesicle transport are related to higher severity. When data associating single SNP genotype and neuron number were analysed, the top two gene variants (rs10869757; p-value = 4.264E-08 and rs185263; p=2.782E-07) were located within the PCSK5 and COMMD10 regions, which also harbor multiple hit SNPs (two for PCSK5 and four for COMMD10) from distinct linkage disequilibrium blocks (r^2<0.9). When correlated with the integrated genetic data, neuronal density differed significantly among the genotype groups in the superior frontal gyrus for all COMMD10, and the pons for all PCSK5 SNPs, demonstrating a protective effect in a minor-allele dose-dependent manner. Using a whole genome approach, we have identified multiple gene variants that associate with the degree of neurodegeneration and clinical outcome in the MS brain. Further work is now required to identify how multiple variants combine to give rise to the heterogeneity in clinical course and pathology.

Disclosures: I. Farkas: None. **Y. Leung:** None. **B. Cooze:** None. **M. Afonso Mota Cruz Pereira:** None. **D. Gveric:** None. **R. Nicholas:** None. **O. Howell:** None. **P. Srivastava:** None. **D. Owen:** None. **R. Reynolds:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.01/E5

Topic: C.01. Brain Wellness and Aging

Support: The Hong Kong Research Grants Council Collaborative Research Fund (Ref: C7069-19G)
The Hong Kong Research Grants Council General Research Fund (Ref: 17600522)
The Hong Kong Research Grants Council Postdoctoral Fellowship Scheme (PDFS2122-7H04)

Title: Resting-state functional connectivity predicts resilience in older adults

Authors: *M. GAO, T. M.-C. LEE;
The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Resilience, the ability to adapt and thrive in adversity, plays a crucial role in maintaining psychological well-being and quality of life in older adults. Predicting resilience in this population provides valuable insights into factors contributing to successful aging, informing the development of interventions to promote resilience. This study aimed to predict resilience based on resting-state functional connectivity (rs-FC) in a sample of 125 right-handed older adults who were free from neurological diseases or psychological illnesses. Resilience was assessed using the Chinese Dispositional Resilience Scale (DRS-15), a tool measuring psychological hardiness and multidimensional (e.g. cognitive, emotional and behavioral) aspects of resilience. Participants with excessive head motion, high depression scores, or incomplete brain scanning were excluded, resulting in a final sample of 99 participants (Female/male: 74/25; Age_{mean} = 66.84). Resting-state fMRI data were preprocessed using standard methods, and brain regions were defined using the Shen 268-node whole-brain functional brain atlas. The 268 × 268 functional connectivity (FC) matrix was extracted for each participant and used in connectome-based predictive modeling (CPM) to predict resilience scores. The results revealed significant predictions of resilience based on rs-FC (positive network: $r = 0.2051$, $p = 0.0417$; negative network: $r = 0.354$, $p < 0.001$). Subsequently, a positive network and a negative network were identified, showing robust positive and negative correlations with resilience, respectively. In the positive network, we found that the FC within the subcortical network, and FC between the subcortical-subcortical, subcortical-default-mode and motor-visual networks contributed the most. In the negative network, we found that the FC within the visual network, and FC between the subcortical-medial frontal, subcortical-motor, subcortical-visual, frontoparietal-motor network contributed the most. These findings demonstrate the potential of rs-FC as predictive markers for resilience in older adults. Moreover, identifying the key networks, including the subcortical, default-mode, motor, and visual networks, offers insights into the neural mechanisms underlying resilience.

Disclosures: M. Gao: None. **T.M. Lee:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.02/E6

Topic: C.01. Brain Wellness and Aging

Support: Hong Kong Research Grants Council CRF (Ref: C7069-19G)
GRF (Ref: 17600522)

Title: Auditory Network-Right Amygdala Connectivity Mediates the Association between Sleep Quality and Levels of Conduct Disorder in Adolescents

Authors: *M. LIU[1,2], M. GAO[2], T. LEE[2];
[1]The Univ. of Hong Kong, Shenzhen, China; [2]The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Abstract Optimal sleep quality is essential for the well-being of adolescents. A high prevalence of sleep problems was reported among adolescents with conduct disorder; however, the underlying neural mechanisms are not well understood. Recent research has indicated that the functional connectivity between cortical regions and the amygdala, a key center for emotional processing, plays a vital role in both sleep quality and conduct disorder. Therefore, the primary objective of this study was to explore whether the association between sleep quality and conduct disorder was mediated by functional connectivity between cortical regions and the amygdala. In this study, data from 3,320 adolescents (52% male, 48% female) were obtained from the longitudinal Adolescent Brain Cognitive Development Study (ABCD), which encompasses data collected across four years (T0: baseline, T1: 1-year-follow-up, T2: 2-year-follow-up, T3: 3-year-follow-up). Participants were aged 9-11 years at T0 (M=9.97, SD=0.62). The Child Behavior Checklist (CBCL) was employed to assess the level of conduct disorders in adolescents, while the Sleep Disturbance Scale for Children (SDSC) was utilized to evaluate sleep quality. Our results revealed that sleep quality ($r=0.278$, $p<0.001$) at T1 and functional connectivity between the auditory network and the right amygdala at T2 ($r=0.059$, $p=0.001$) were significantly associated with the level of conduct disorder. The mediation model indicated that poor sleep quality at T1 increased the level of conduct disorder at T3, mediated by the hyperactivation of the functional connectivity between the auditory network and right amygdala at T2 (mediation effect size=0.0015, BootSE=0.0008, BootCI = [0.0002, 0.0031]). Our results underscore the importance of sleep quality in developing conduct disorders in adolescents and highlight the mediation role of specific brain functional connectivity in this association. These findings emphasize the need for interventions and strategies that focus on improving sleep habits and managing conduct disorder among adolescents.
Funding Information: The work is supported by The Hong Kong Research Grants Council CRF (Ref: C7069-19G) and GRF (Ref: 17600522)

Disclosures: M. Liu: None. **M. Gao:** None. **T. Lee:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.03/E7

Topic: C.01. Brain Wellness and Aging

Support: The Hong Kong Research Grants Council Collaborative Research Fund (Ref: C7069-19G)

Title: Associations between Measures of Mental Health, CAGE-AID Scores, and Addiction Risk: Implications for Screening and Intervention models

Authors: *S. YANG;
Hong Kong Univ., Hong Kong, China

Abstract: This study aimed to investigate the associations between CAGE-AID scores, a tool used for drug and alcohol use screening, and measures of mental health and addiction risk. The Mental Disorder Questionnaire (MDQ), Psychosis Questionnaire-16 (PQ-16), and South Oaks Gambling Screen (SOGS) were employed to assess bipolar disorder risk, psychotic vulnerability, and pathological gambling, respectively. Understanding these associations can provide valuable insights into the identification and management of individuals at risk for mental health disorders and addiction problems. The study sample consisted of 18 participants (Agemean=25.06, female/male:11/7). Participants completed the CAGE-AID, MDQ, PQ-16, and SOGS as part of a comprehensive assessment battery. Correlation analyses were conducted to examine the relationships between CAGE-AID scores and the aforementioned measures. The results revealed significant positive associations between CAGE-AID scores and MDQ scores ($r = 0.602$, $p < 0.01$), suggesting a strong link between drug and alcohol use screening and bipolar disorder risk. Additionally, a significant positive correlation was found between CAGE-AID scores and PQ-16 scores ($r = 0.527$, $p < 0.05$), indicating an increased likelihood of psychotic vulnerability among individuals with higher substance use screening scores. Furthermore, CAGE-AID scores showed a significant positive association with SOGS scores ($r = 0.714$, $p < 0.001$), implying a heightened risk of pathological gambling among those with elevated drug and alcohol use screening scores. These findings underscore the importance of integrating substance use screening tools like CAGE-AID into comprehensive assessments for mental health and addiction risk. The positive associations found between CAGE-AID scores and MDQ, PQ-16, and SOGS scores suggest potential shared underlying factors or comorbidity between substance use, bipolar disorder, psychotic vulnerability, and pathological gambling. Early identification of individuals at risk can facilitate targeted interventions and prevention efforts, enabling early identification and appropriate management of individuals at risk for bipolar disorder, psychotic vulnerability, and pathological gambling. Future research should explore these relationships in larger and more diverse samples to enhance our understanding and inform tailored interventions for at-risk populations.

Disclosures: S. Yang: None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.04/E8

Topic: C.01. Brain Wellness and Aging

Support: NSF Grant BCS- 2122866
Neuroscience Research Center
MCW New Faculty Award

Title: Compensatory Neural Mechanisms Mediate Cognitive Deficits in Patients with Age-related Hearing Loss.

Authors: *G. GURARIY[1], S. MLEZIVA[2], L. ELLIOTT[1], S. ZIADEH[1], K. KOZLOWSKI[2], M. S. HARRIS[2], A. S. GREENBERG[1];
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Abstract: The increasing prevalence of age-related hearing loss is becoming a significant public health issue, especially considering the expanding demographic of older adults. The correlation between hearing loss and cognitive decline is well-established, as evidenced by extensive epidemiological data. Two hypotheses currently predominate regarding the nature of this relationship. The first, known as the *sensory deprivation hypothesis*, posits that the brain undergoes potentially irreversible changes due to reduced sensory stimulation. In contrast, the *information degradation hypothesis* suggests that the ambiguity of auditory signals necessitates the allocation of additional cognitive resources, which are consequently diverted from other cognitive processes. Unlike the sensory deprivation hypothesis, the information degradation hypothesis implies that cognitive decline could be reversed once auditory function is restored. To gain a deeper understanding of the connection between hearing loss and cognitive decline, we tested patients with untreated hearing loss who were eligible for cochlear implant (CI) surgery but had not yet undergone the procedure (PreCI group). We also included a group of age-matched individuals with normal hearing (Control group). To evaluate cognitive function, we employed the N-back visual working memory paradigm. Participants were asked to perform a behavioral version of the N-back experiment, where the memory load was incrementally increased from 1 to 3 items. In addition, participants performed the N-back experiment during functional Magnetic Resonance Imaging (fMRI), which was used to measure the Blood Oxygen Level Dependent (BOLD) signal during N=1 and N=2 blocks. Behavioral results showed no significant differences between the PreCI and Control groups. This finding suggests that there is no apparent evidence of cognitive decline in subjects with age-related hearing loss based on this measure. However, fMRI results (extracted timecourses) revealed that the level of activation in the intraparietal sulcus was significantly larger in the N=2 condition compared to the N=1 condition, but only in the PreCI group. These findings suggest that the absence of behavioral differences may be attributed to compensatory mechanisms within the parietal cortex by which the brain adaptively reallocates resources to maintain cognitive function. This study underscores the complexity of the relationship between age-related hearing loss and cognitive decline, and the potential role of compensatory mechanisms in the attenuation of cognitive deficits.

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Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.05/E9

Topic: C.01. Brain Wellness and Aging

Support: The Hong Kong Research Grants Council GRF (Ref: 17600522)

Title: Unraveling the interplay between education, intrinsic functional connectivity and cognitive planning in healthy ageing

Authors: *M. CHEN, T. LEE;
the Dept. of Psychology, The Univ. of Hong Kong, Hong Kong, China

Abstract: Unraveling the interplay between education, intrinsic functional connectivity and cognitive planning in healthy ageing**Authors*Menglu Chen**, Tatia M.C. Lee; The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong**DisclosuresMenglu Chen**: None. **Tatia M.C. Lee**: None.The work is supported by The Hong Kong Research Grants Council GRF (Ref: 17600522)**Abstract**Ageing is associated with brain intrinsic functional connectivity (FC) changes and cognitive decline. While the positive relationship between education and cognitive performance is well established in older adults, the neural mechanisms underpinning this relationship still need to be fully understood. Cognitive planning, the ability to set goals and develop strategies, is critical in daily functioning and independence among older adults. Specifically, the research question of how early life education affects brain networks' intrinsic FC and people's cognition planning has not yet been fully addressed. To uncover this research question, we recruited 102 healthy ageing individuals aged from 60 to 79 years old to complete a resting-state functional magnetic resonance imaging (fMRI) scanning. We assessed their early life education years and cognitive planning using the well-characterized planning test: Tower of London task. We calculated the intrinsic functional connectivity using the Power 264 template and then examined the relationship between education years, intrinsic FC, and cognitive planning. We found that education was positively correlated with the FC between default mode network (DMN) and ventral attention network (VAN) ($r = 0.231$, $p = 0.02$). This suggests that ageing individuals with longer early-life education may have higher intrinsic DMN-VAN FC. We also found a negative correlation between the total move in the Tower of London task and DMN-VAN FC ($r = -0.206$, $p = 0.03$), indicating that higher DMN-VAN connectivity was associated with better cognitive planning. Moreover, we discovered that DMN-VAN FC fully mediates the relationship between education experience and cognitive planning (Indirect effect $\beta = -0.19$). Specifically, individuals with longer early life education years had higher DMN-VAN connectivity, leading to less move in the Tower of London task, representing better cognitive planning performance. Our findings reveal

that early life education experience is associated with enhanced intrinsic FC between DMN and VAN, potentially improving cognitive planning in healthy ageing individuals. These results emphasize the protective role of education in preserving brain function and cognitive performance during the ageing process.

Disclosures: M. Chen: None. **T. Lee:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.06/E10

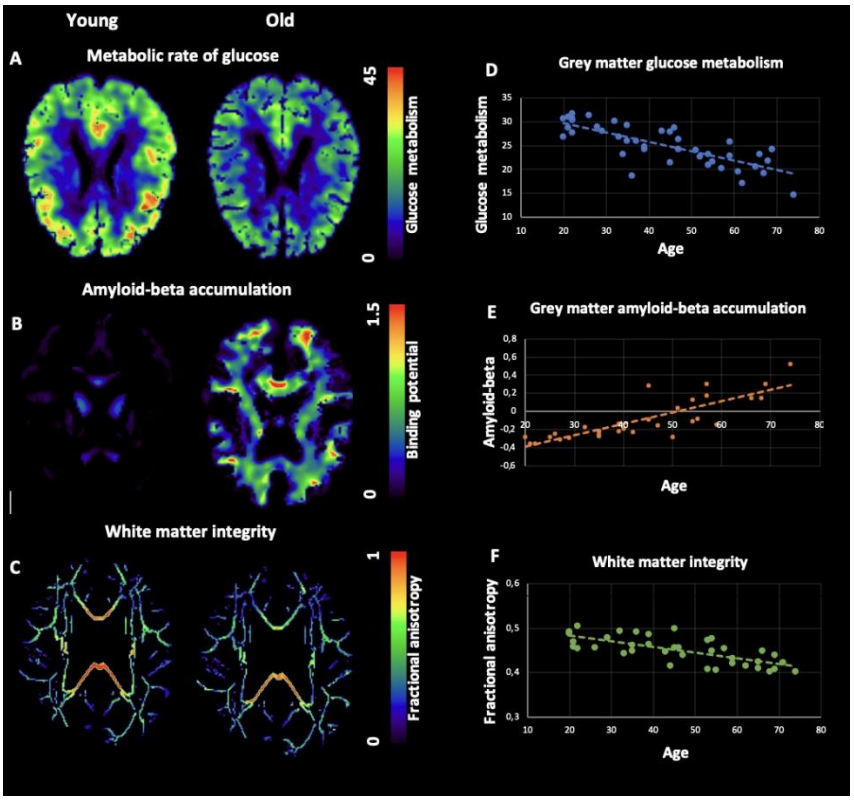
Topic: C.01. Brain Wellness and Aging

Support: Psychiatric Research Funding, Southern Region of Denmark

Title: Neurobiology of healthy aging

Authors: *M. SEYEDI VAFAEE, L. VIND KNUDSEN, T. MICHEL;
Psychiatry Res., Univ. of Southern Denmark, Odense, Denmark

Abstract: Purpose: Decrease in neurogenesis, increase of mitochondrial malfunction, and as a result, impaired energy metabolism and increase of beta amyloid (Aß) plaques are held to be key mediators of aging and age-related neurological disorder. We aimed to investigate the interplay between cerebral glucose metabolism, and increased Aß plaques and its effect on grey matter density and white matter integrity.
Methods: Eighty healthy subjects between 20-80 years underwent one ^{11}C-PiB and one ^{18}F-FDG PET scans and a series of simultaneous MRI scans including arterial spin labeling (ASL) and diffusion tensor imaging (DTI) scans for the measurement of cerebral blood flow (CBF) and white matter integrity (WMI) accordingly.
Results: Our study showed a positive correlation between increases of age and deposition of Aß plaques, especially in the so-called AD signature regions such as hippocampus, posterior cingulate gyrus and orbitofrontal cortex. Moreover, cerebral glucose metabolism as an index of neuronal activity revealed a strong negative correlation between age and grey matter (GM) density, interestingly in similar regions as Aß deposition occurred, hinting that increases in Aß plaques have detrimental effects on GM in these regions. Results of ASL-MRI also supported these findings as CBF and metabolism appeared to be negatively associated with age, and again appeared to overlap with the aforementioned regions. Diffusion tensor imaging (DTI) demonstrated that WMI decreases with age and interestingly, in the same regions that amyloid deposition has occurred.
Conclusion: These findings implies that Aß plaques deposition causes deterioration of WMI and thereby loss of brain connectivity and could cause decreases in GM density, metabolism, and CBF, resulting in pathogenesis of neurodegeneration.



Disclosures: **M. Seyedi Vafaee:** None. **L. Vind Knudsen:** None. **T. Michel:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.07/E11

Topic: C.01. Brain Wellness and Aging

Title: Mri texture analysis of the aging brain

Authors: ***M. KHOURY**[1,2], N. CHURCHILL[3], S. J. GRAHAM[4], C. FISCHER[5], D. MUNOZ[6], T. SCHWEIZER[7];
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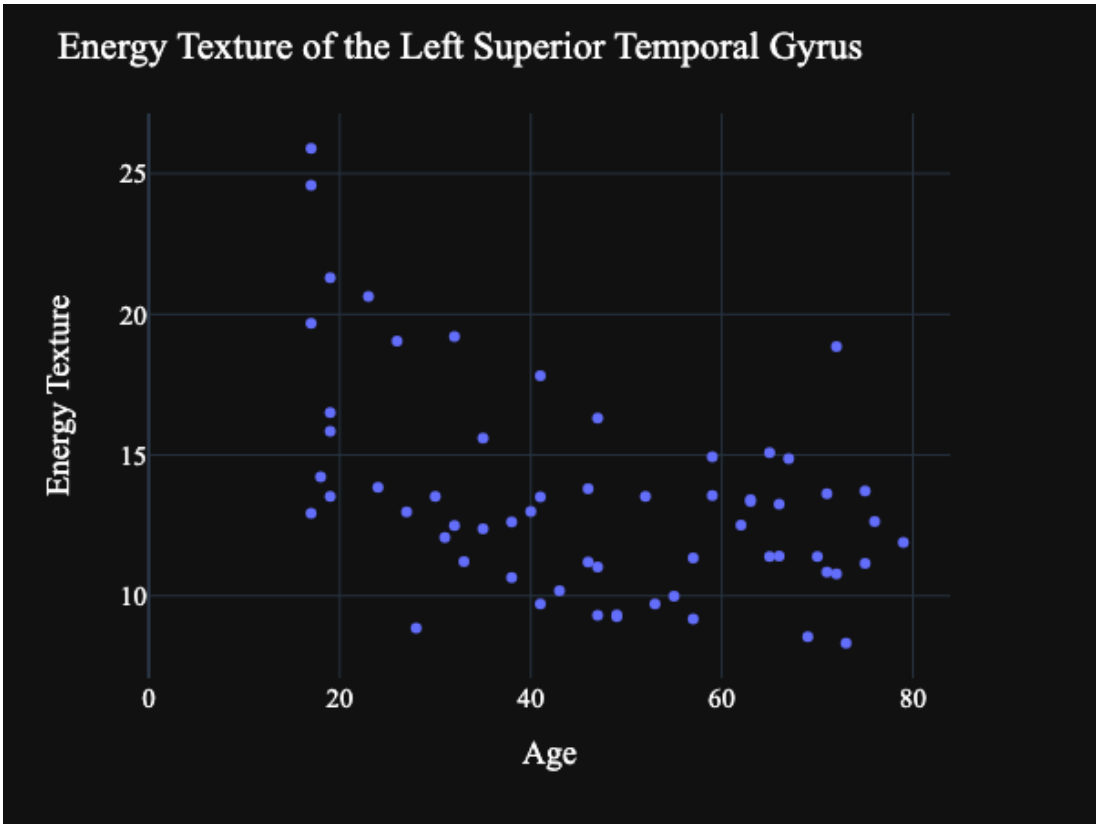
Abstract: A fundamental objective of texture analysis in magnetic resonance imaging (MRI) is the detection of subtle changes in tissue microstructure, based on patterns of local signal intensity. Given age-related changes in neurophysiology, such as cortical atrophy and vascular

aging, it is likely that these measures vary with age; however, this has not yet been directly evaluated. The present study investigates MRI texture of the normal aging brain; we hypothesize that with increasing age, texture homogeneity and energy decline, while entropy shows an opposite pattern of increase. A total of 61 healthy participants (Mean(SD) age: 46.6 (9.2) yrs., Range: 17 - 79 yrs) were recruited and imaged at a single site, with a T1-weighted MRI scan (1mm resolution) collected. Freesurfer v7.2.0 was used to obtain segmentation maps of grey matter (GM) and white matter (WM) regions in the participant's native space. A 3D-Grey-Level-Co-Occurrence Matrix (GLCM) approach was applied for GM and WM matter parcels with 7 Haralick texture features calculated at each region of interest: Energy, Entropy, Contrast, Homogeneity, Correlation, Cluster Shade, and Cluster Prominence. Average regional texture feature scores were then regressed against demographic variables of age and sex, with a bootstrapped ratio z-score (Z) calculated. Across all GM and WM regions, significant decreases with age were seen for Homogeneity (GM Z=-4.2, WM Z=-3.4) and Energy (GM Z=-1.8, WM Z=-2.3). Conversely, significant increases with age were seen for Entropy (GM Z=2.3, WM Z=1.8) and Contrast (GM Z=4.3, WM Z=3.3). Effects were non-significant for Correlation, Cluster Shade and Prominence. Our study indicate systematic changes in tissue texture of T1-weighted scans as a function of age. As age increases, voxels show larger, more spatially variable changes in signal intensities, reflected in decreased Energy and Homogeneity, and increased Entropy and Contrast. Future research should incorporate this information into texture models, when identifying texture biomarkers of disease and injury in patient cohorts.



Disclosures: **M. Khoury:** None. **N. Churchill:** None. **S.J. Graham:** None. **C. Fischer:** None. **D. Munoz:** None. **T. Schweizer:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.08/E12

Topic: C.01. Brain Wellness and Aging

Support: 1R01AG053961 (NIH/NIA)

Title: Plasma p-tau positivity affects cognitive and network flexibility in the medial temporal lobe among healthy older african americans

Authors: *M. BUDAK[1], B. A. FAUSTO[1], Z. OSIECKA[1], M. SHEIKH[1], R. PERNA[1], N. J. ASHTON[2], K. BLENNOW[2], H. ZETTERBERG[2], M. A. GLUCK[1];
[1]Rutgers Univ. Behavioral and Neural Sci., Newark, NJ; [2]Dept. of Psychiatry and Neurochemistry, Univ. of Gothenburg, Göteborg, Sweden

Abstract: Recent studies have suggested that p-tau levels in plasma may provide an affordable and minimally invasive tool to evaluate Alzheimer's disease (AD) pathophysiology. We have previously shown that individuals with preclinical AD have deficits in generalization of past learning to subsequent task demands several years preceding overt clinical symptoms of AD. Medial temporal lobe (MTL) dynamic network flexibility—a putative resting-state functional Magnetic Resonance Imaging (rs-fMRI) biomarker of AD—is correlated with generalization performance. The present study investigated the putative association between of plasma p-tau positivity (or negativity) on the relationship between MTL dynamic network flexibility and generalization performance in a cognitively healthy older African American cohort. The cohort included 67 older, cognitively normal African Americans (M_{age} = 68.40 years, SD =6.38; M_{edu} = 14.09 years, SD = 2.32; n = 48 women), who provided blood samples, completed cognitive tasks, and a rs-fMRI session. Participants' normal cognitive status was confirmed using the Mini-Mental State Examination (MMSE) (M_{MMSE} =27.66, SD_{MMSE} = 2.09) and generalization performance was assessed using the Rutgers Acquired Equivalence Task. Plasma was extracted from blood samples to assess p-tau181 and p-tau231 levels using Single molecule array technology, measured by in-house Simoa methods at University of Gothenburg. Based on the sample median thresholds, a subset of participants was characterized as p-tau positive (≥16.9 for p-tau181 and ≥17.5 for p-tau231). There was a significant positive correlation between MTL dynamic network flexibility and generalization performance only among participants with a negative p-tau231 status (r=0.378, p=0.033) and a negative p-tau181 status (r=0.497, p=0.004). Specifically, participants with a negative p-tau231 status and a negative p-tau181 status showed higher MTL dynamic network flexibility with better generalization performance. There was no significant relationship between MTL dynamic network flexibility and generalization performance among participants with a positive p-tau231 status or a positive p-tau181 status. Generalization and MTL dynamic network flexibility may capture early cognitive dysfunction associated with AD, but only prior to the accumulation of AD-type tau pathophysiology as indexed by plasma p-tau markers.

Disclosures: **M. Budak:** None. **B.A. Fausto:** None. **Z. Osiecka:** None. **M. Sheikh:** None. **R. Perna:** None. **N.J. Ashton:** None. **K. Blennow:** None. **H. Zetterberg:** None. **M.A. Gluck:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.09/E13

Topic: C.01. Brain Wellness and Aging

Support: NIH/NCCIH R33AT009310-05S1

Title: Evaluation of the impact of musculoskeletal pain on brain age using data from the UK Biobank

Authors: *M. CANNISTRA[1], V. SACCA[2], G. TRADIGO[3], N. TODOROVA[2], P. VELTRI[4], T. GE[2], J. KONG[2];
[1]Psychiatry, Massachusets Gen. Hosp., Boston, MA; [2]Psychiatry, Massachusetts Gen. Hosp., Boston, MA; [3]E-Campus Univ., Novedrate (Como), Italy; [4]Univ. of Calabria, Cosenza, Italy

Abstract: Purpose: The aim of this study was to investigate how chronic musculoskeletal pain may influence brain aging as compared to age and gender matched pain-free healthy controls using structural (T1) and diffusion (DTI) features from UK Biobank dataset.**Methods:** Data sets associated with chronic musculoskeletal pain (Back N. 967, Hip N. 252, Knee N. 1078, and Neck N. 987) and healthy controls (N. 5064) were identified and extracted from UK Biobank. A LASSO model was built and trained on the healthy cohort using features extracted from T1 and DTI sequences. Mean Absolute Error (MAE) metric was obtained using a 10-fold cross-validation on the control subjects. Then the model was tested on the remaining pain sets with the calculation of MAE for each of them. Predictions were analyzed and compared between different groups of subjects. Brain age prediction gaps (difference between real age and predicted age) were extracted and used for statistical analysis (two sample t-test) between chronic pain and control subjects.**Results:** In musculoskeletal pain groups, predictions showed brain shrinkage indicative of brain aging at a greater rate than was observed in the healthy controls, especially in neck/shoulder pain. Statistical analysis on the prediction gaps showed significant differences between chronic musculoskeletal pain and healthy controls using both T1 and DTI features ($p= 0.04$). Further analyses showed a significant difference between the two groups using only DTI features ($p< 0.01$), and no significant finding when using only T1 features ($p= 0.08$). Subgroups analysis showed significant results in the comparison between neck and healthy subjects in all imaging modalities (T1+DTI, $p<0.001$; T1, $p<0.001$; DTI, $p<0.001$), in the comparison between back pain and healthy controls using only DTI ($p= 0.048$), and between hip pain and healthy controls (T1+DTI, $p= 0.049$; T1, $p=0.02$). **Conclusion:** Using a community-based dataset, we found that individuals with musculoskeletal pain (particularly the neck/shoulder pain) are

associated with an older brain in comparison with age and gender matched pain-free controls.
AcknowledgeFunding: This project is supported by NIH/NCCIH R33AT009310-05S1.

Disclosures: M. Cannistra: None. **V. Sacca:** None. **G. Tradigo:** None. **N. Todorova:** None. **P. Veltri:** None. **T. Ge:** None. **J. Kong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JK holds equity in two startup companies (MNT, BTT) and a patent on applying neuromodulation, but declares no conflict of interest.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.10/E14

Topic: C.01. Brain Wellness and Aging

Title: Untangling age and menopausal status reveals no differences in white matter hyperintensity volume in pre- and post-menopausal females

Authors: *D. WEZEL[1,2], O. PARENT[1,3], M. COSTANTINO[1,3], G. PIGEAU[1,3], G. A. DEVENYI[1,4], M. CHAKRAVARTY[1,3,4,5];
[1]Cerebral Imaging Centre, Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [2]Res. Master Cognitive Neuropsychology, Vrije Univ. Amsterdam, Amsterdam, Netherlands; [3]Integrated Program in Neurosci., [4]Dept. of Psychiatry, [5]Dept. of Biomed. Engin., McGill Univ., Montreal, QC, Canada

Abstract: White matter hyperintensities (WMHs) are radiological abnormalities indicative of cerebrovascular dysfunction. They are associated with increased risk for cognitive decline and their prevalence increases with age. Females are affected more than males, especially in later life. A leading hypothesis regarding this sex difference is that the protective effects of female sex hormones minimize during the menopausal transition. However, untangling the effects of age and menopause is highly difficult since menopause is an age-dependent event. Here, we conduct a large cross-sectional study using data from the UK Biobank to investigate differences in WMH volumes across the menopausal transition using a strict age-matching procedure. We further investigate if lifestyle factors have the same protective effects on brain health before and after the menopausal transition.A large sample of females (n = 13,999) from the UK Biobank was investigated. After strict age-matching (MatchIt R-package), 212 premenopausal (PRE), 419 naturally postmenopausal (NAT), and 210 surgically-induced postmenopausal (SURG) females were included. Using linear models, the relationships between WMH volume (log-transformed and normalized for total brain volume) and menopausal status, as well as age at menopause were investigated, correcting for income and age. We further investigated if the effect of cardiovascular risk factors (17 variables regarding blood pressure, diabetes, obesity, smoking, physical activity and alcohol consumption) on WMH volumes differed between groups.Overall, we found no difference in WMH-volume load in PRE relative to NAT (p = .941, β; = -.006) or

SURG (p = .420, β; = .078). Age at menopause had a significant but small effect only in the NAT group (p = .016, β; = -.019). There was no effect of hormone replacement therapy on WMH volumes (NAT: p = .159, β; = .024, SURG: p = .686, β; = -.030). Few interactions between lifestyle factors and WMH volumes by menopausal group were significant at the $p <$ 0.05 level (only for blood-pressure medication, diabetes, and two physical activity-related risk factors).In one of the largest and well-powered studies of its kind, we demonstrate that by isolating the effect of menopausal transition from aging there is no impact of the menopausal transition on WMH-burden. We further show that the potentially protective effect of positive lifestyle factors on brain health does not change after menopause, with a few exceptions. These results suggest, contrary to previous studies in small samples, that factors other than the menopausal transition are likely at play in explaining the difference in WMH burden between males and females in later life.

Disclosures: D. Wezel: None. **O. Parent:** None. **M. Costantino:** None. **G. Pigeau:** None. **G.A. Devenyi:** None. **M. Chakravarty:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.11/E15

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant OD-011092
NIH Grant NIA/OD-011092

Title: Elevated aquaporin-1 expression in brains of old and oldest-old rhesus macaques

Authors: O. STAYER-WILBURN[1], D. I. BROWN[2], S. SRINIVASAN[1], B. PARK[3], D. ROSENE[4], P. SHULTZ[4], A. VITANTONIO[4], C. DIMOVASILI[4], J. MATTISON[5], K. VAUGHAN[5], H. URBANSKI[1], *S. KOHAMA[1];
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Abstract: Aquaporin-1 (AQP1) is a common water channel protein that enables cellular osmoregulation and water transport across tissues. AQP1 in the adult human and non-human primate (NHP) brain is found in the choroid plexus and on astrocytes in the white matter (WM), glial limitans, and around pial blood vessels. Cortical AQP1 increases in neuropathologies like Alzheimer's disease (AD), where it is thought to regulate Amyloid beta (Aβ) plaque deposition. AQP1 expression is also observed in normal, aged human cortices, yet is undescribed in aged NHP brains. The current study leverages the National Institute of Aging (NIA) longitudinal study of caloric restriction (CR), which includes old and oldest-old rhesus monkeys. Aspects of this species make it a translational model of normative aging. We hypothesized that AQP1

expression is elevated in extremely aged rhesus brains, potentially regulated by CR and interacting with Aβ. Paraformaldehyde-fixed sections of prefrontal (PFC) and temporal cortices (TC) from 36 rhesus macaques (mixed sex, 22 to 44 years, +/- CR) were mounted for antigen retrieval, then underwent immunohistochemistry to label AQP1 (rabbit anti-AQP1, Proteintech, Rosemont, IL), using the ABC-DAB method. Percent area coverage and integrated density of AQP1 staining were measured sub-regionally using ImageJ free-ware. The results were analyzed for effects of age, sex, and +/-CR. Additional PFC sections were fluorescently double-labeled to confirm colocalization between AQP1, and astrocytic markers (Mouse anti-Glial Fibrillary Acidic Protein / Vimentin from SC biotechnologies, Santa Cruz, CA) or Aβ (4G8, BioLegend). AQP1 expression in the NHP brain partially matched previous reports, yet additional astrocyte phenotypes were seen in cortical and subcortical areas. In the TC, sub-regional AQP1 area coverage was unaffected by age, although intensity in the hippocampus increased with age ($p=0.016$). The hippocampus had the greatest percent area coverage of AQP1 in all regions of interest besides white matter, of both lobes in the analysis. In the PFC,
four sub-regions showed an increase in both AQP1 area and intensity with age ($p<0.05$). In fluorescence experiments, astrocytic GFAP and vimentin overlapped with AQP1. Plaque-like AQP1 colocalized with astrocyte markers, near Aβ plaques. In sum, the rhesus brain shows a regional increase of AQP1 expression in old and oldest-old ages, with no effect of treatment or sex. AQP1 expression in the oldest-old NHP brain mimics aspects of human neuropathology, contributing to a progressive shift in the brain towards overt neuropathology that involves dysregulated astrocytic water channels.

Disclosures: O. Stayer-Wilburn: None. **D.I. Brown:** None. **S. Srinivasan:** None. **B. Park:** None. **D. Rosene:** None. **P. Shultz:** None. **A. Vitantonio:** None. **C. Dimovasili:** None. **J. Mattison:** None. **K. Vaughan:** None. **H. Urbanski:** None. **S. Kohama:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.12/E16

Topic: C.01. Brain Wellness and Aging

Title: Rewiring alternative splicing of TRAIL-R4 to enhance neurons survival.

Authors: *C. POIRIER, B. LAURENT;
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Abstract: Background. TNF-related apoptosis-inducing ligand (TRAIL), a cytokine secreted by most normal tissues, causes apoptosis by binding to specific death receptors. TRAIL binds to the TRAIL-R1 and TRAIL-R2 death receptors to activate downstream apoptotic pathways, but it can also bind the TRAIL-R3 and TRAIL-R4 receptors, which function as TRAIL-neutralizing decoy-receptors. TRAIL-R4 expression protects neurons from TRAIL-induced apoptosis and enhances neurons survival. The exon 3 of TRAIL-R4 gene can be alternatively spliced. The absence of this

exon 3 within the final mRNA leads to the truncation of ligand-receptor domain. This alternative splicing modifies TRAIL affinity for its receptor to potentially favor TRAIL binding to other cell death receptors and promote apoptosis.
Hypothesis and objectives. The splicing mechanism could be dysregulated during aging and in neurodegenerative pathology and could potentially lead to neurons death. Our goals are 1/ to decipher the molecular mechanisms regulating TRAIL-R4 splicing, and 2/ to investigate the impact of this TRAIL-R4 isoform (isoTRAIL-R4) in the apoptosis of neurons cells.
Research approach. At first, we determined the molecular mechanisms underlying TRAIL-R4 splicing. We identified that two Alu elements in opposite orientation within the intron flanking the spliced exon, could influence exon inclusion. To address the functional relevance of Alu elements in TRAIL-R4 splicing, we constructed a mini-gene containing exons 2 through 4 of TRAIL-R4 gene and deleted each Alu element. The results showed that deletion of each Alu element increases the TRAIL-R4 exon 3 skipping, confirming that Alu elements are important regulators of TRAIL-R4 splicing. We next demonstrated that the transcription factor GATA3 could regulate TRAIL-R4 splicing through its binding to Alu elements, and that its overexpression or inhibition modulates the TRAIL-induced programmed cell death. Finally, we determined that neurons overexpressing isoTRAIL-R4 are more sensitive to the TRAIL-induced cell death, hence supporting our hypothesis.
Perspectives. Our findings showed that modulating TRAIL-R4 splicing can enhance apoptosis of neurons cells. With the help of antisense oligonucleotides and molecules with high clinical potential, we wish to rewiring the molecular mechanisms of isoTRAIL-R4 expression to its main form and contribute to the protection of neurons.

Disclosures: **C. Poirier:** None. **B. Laurent:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.13/E17

Topic: C.01. Brain Wellness and Aging

Support: Ministry of Transportation Ontario
CIHR Grant 310697

Title: The Neural Substrates of the Porteus Maze Task in a Cognitively Normal Aging Cohort

Authors: *N. J. MIRZA[1,3], T. A. SCHWEIZER[1,3], N. W. CHURCHILL[4,5], S. J. GRAHAM[6,2], F. TAM[7];
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Abstract: The Porteus Maze Test (PMT) provides measures of executive functioning including planning, processing speed and foresight. The PMT has been used to assess prefrontal cortex activity in various neurological conditions, such as Alzheimer's disease and pathological aging. Despite its widespread clinical use, the neural basis for PMT performance remains largely unknown. The objective of this study was therefore to characterize the neural substrates of the PMT in healthy adults using a novel MR-compatible tablet. A total of 29 healthy, cognitively normal adults between the ages of 50-89 (mean age: 70 ± 10.2, 12 female) were imaged on a 3T MRI system (Siemen Skyra) at St. Michael's hospital. Inside the MRI scanner, participants used a novel MRI-compatible table and stylus to perform the PMT, along with by a "control" task where they traced a solved maze. Images of brain activity were obtained using fMRI during both tasks. In addition, task completion times were recorded via video playback of behavioural data. Afterwards, brain activity was measured for maze and control tasks at the subject level via general linear model (GLM), and group-level activation maps obtained via voxel-wise GLMs that included covariates for age and task completion time. During the maze task, participants showed increased activity in frontal-parietal regions, such as the cuneus and frontal gyri, with greater magnitude and extent than seen in the control task. Reduced activity during the maze task was also seen in the right caudate, cingulate gyrus, and thalamus. Increasing age was associated with greater activation in the cingulate, left caudate, hippocampi and frontal areas. Moreover, longer task completion times were associated with greater activation in the left angular gyrus. Overall, this study identified for the first time the neural basis for PMT performance, with increased activity seen in frontal-parietal regions of the brain, including the superior parietal lobes, cingulate, cuneus and precuneus, and the frontal gyri. The study identified effects of healthy aging and speed of task performance on PMT-related brain activity. These findings provide new insights into this widely-used neurocognitive assessment.

Disclosures: N.J. Mirza: None. **T.A. Schweizer:** None. **N.W. Churchill:** None. **S.J. Graham:** None. **F. Tam:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.14/E18

Topic: C.01. Brain Wellness and Aging

Support: 2022R1F1A1061216

Title: Quercetin inhibits cerebral blood flow reduction through the suppression of cerebrovasvular detoriation in aging

Authors: *J. MUN[1], C. PARK[2];
[1]Dept. of Biomed. Science, Grad. Sch., Kyunghee Univ., Seoul, Korea, Republic of; [2]college of medicine, Kyung Hee Univ., Sch. Medicine, Kyunghee Univ., Seoul, Korea, Republic of

Abstract: Cerebrovascular alterations with advancing age are accompanied by an increase in cerebrovascular dysfunctions such as a decrease in cerebral blood flow and an increase in permeability of the blood-brain barrier (BBB). Quercetin, as a natural bioflavonoid, has positive effects in anti-aging to exhibit anti-oxidant and anti-inflammatory activities. This study aimed to elucidate the effect of quercetin on attenuating the age-related decline in cerebral blood flow and to identify the associated factors modulating cerebrovascular degeneration in mice. Administer of quercetin (orally administered for 4 weeks) could suppress reduce of cerebral blood flow compared to same-age normal aging mice (13 months old). Moreover, quercetin suppressed age-related morphological alterations such as increased of vessel tortuosity, thinned string vessels, and deformed vessels. An assessment of BBB permeability using Evans Blue showed quercetin reduced age-related increases in leakage of BBB. The results of the western blot showed that quercetin increased SIRT1, SIRT6, BBB tight junction protein (Claudin-5), and endothelial cell regulator (eNOS and Tie2) in microvessel. These results suggest that quercetin might ameliorate age-related cerebrovascular alterations by mitigating endothelial dysfunction via increasing SIRT1/SIRT6 in microvessels.

Disclosures: J. Mun: None. **C. Park:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.15/E19

Topic: C.01. Brain Wellness and Aging

Support: NIH NINDS R01NS114651
PHS Grant K12GM111726

Title: Age-dependent remodeling of neocortical motor outputs in 5xfad mice

Authors: R. M. BROWN, II[1], ***C. WOLSH**[2], A. SAGUI[1], E. M. OCHOA[1], J. A. BOYCHUK[1]; [1]Cell. and Integrative Physiol., UT Hlth. San Antonio, San Antonio, TX; [2]UT Hlth. Sci. Ctr. San Antonio Dept. of Neurosci., San Antonio, TX

Abstract: In mammals, the neocortex provides descending motor outputs (eg., corticospinal tract) that underpin skilled volitional movement. Here, we determined the functional organization of complex neocortically-driven movement in 5XFAD mice and wild-type control (WT Control) mice at either 3, 6 or 9-12 months of age to test the effects of aging and phenotypic progression of these groups. The 5XFAD model over-expresses 3 mutations of human amyloid beta (A4) precursor protein 695 (APP) and 2 mutations of presenilin 1 (PSEN1) that are associated with Familial Alzheimer's Disease (FAD). Motor behavior was assessed using the rotarod test. Long-duration intracortical microstimulation (LD-ICMS) was systematically applied to neocortex to evoke "complex" (multi-joint) movements that appear to match the timescale of brain activation, and motor characteristics of awake-behavior. LD-ICMS

in these mice produced 4 types of complex forelimb movement: ADVANCE, RETRACT, ELEVATE and DIG. These movements were highly organized, rather than stochastic, occupied discrete territories of neocortex and may represent basic components of forelimb motor behavior in this species. LD-ICMS also produced 4 types of simple movement: DIGIT, WRIST, ELBOW and SHOULDER in these animals. Movement types and their neocortical topography were not significantly different between 5XFAD mice and WT Controls at 6 months of age. In contrast, at 12 months of age the overall neocortical area of complex movements and specific zones of complex ADVANCE and DIG were significantly reduced in 5XFAD mice. Relative to WT Controls, simple neocortical motor outputs were significantly increased in 6-month-old 5XFAD mice whereas these movement types were significantly decreased in 5XFAD mice at 12-months of age; this included specific decreases in simple SHOULDER and WRIST. Thus, 5XFAD mice exhibit age-dependent remodeling of neocortical motor outputs. 5XFAD mice also travelled significantly greater distances during rotarod testing that may be due to a hyper-active motor phenotype. Ongoing testing is comparing neocortical and corticospinal anatomy of these groups at these time-points in order to contextualize these physiological findings. The possible hyper-active motor phenotype is being tested by quantifying motor activity using additional behavioral measures. Together, the long-term goal of this study is to determine possible time-points and mechanisms for diagnostic and interventional purposes of neocortical motor control in FAD and related disorders.

Disclosures: **R.M. Brown:** None. **C. Wolsh:** None. **A. Sagui:** None. **E.M. Ochoa:** None. **J.A. Boychuk:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.16/Web Only

Topic: C.01. Brain Wellness and Aging

Support: NRF Grant 2023R1A2C2006894
NRF Grant 2021R1A6A3A01088243

Title: Altered biomechanical force regulates astrocyte function and behavior in aged brain

Authors: *O. KIM, H. LEE;
Chung Ang Univ., Seoul, Korea, Republic of

Abstract: It has been known that the secretion and replacement rate of cerebrospinal fluid (CSF) are reduced in the aging population. Although this weakening of the CSF flow may induce altered signaling to brain cells and tissues, detail mechanism has not been clearly understood so far. Here, we simulated the aged brain microenvironment by varying the fluid flow. Mouse primary astrocytes were observed in a CSF mimicking microfluidic environment, and their behavior was examined under varying shear stress condition. We found that reduced shear stress

resulted in decreased astrocyte motility and altered protein and gene expression profiles. Specifically, shear stress reduced the protein and gene expression of glial fibrillary acidic protein (GFAP), which is one of the activation markers of astrocyte following damage or stress in the central nervous system. In addition, the expression of neurotoxic or proinflammatory markers associated with the A1 phenotype, such as srgn and H2D1, was decreased. Moreover, reduction of shear stress induced increased senescence-related b-galactosidase activity and upregulation of several senescence-related genes such as CD38, p16, and p53 in astrocytes. Taken together, this study is the first attempt to confirm the response of astrocytes to shear stress and to explore the relationship between aging and biomechanical forces.

Disclosures: O. Kim: None. **H. Lee:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.17/E20

Topic: D.05. Auditory & Vestibular Systems

Support: NIH/NIDCD R01 DC017708

Title: Age-related Increase of Dense Core Vesicles in the Central Nucleus of the Inferior Colliculus

Authors: A. P. OHL[1], J. BUSBY[1], S. R. DUNCAN[1], L. S. ALMASSRI[1], A. WAWRZYNIAK[1], M. C. IAFRATE[1], D. ALBABA[1], B. VEGA[1], E. A. SLABINSKI[1], A. M. BEAVER[1], A. M. MAFI[2], M. BUERKE[3], J. W. YOUNG[1], ***J. G. MELLOTT**[1];
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Abstract: While examining the ultrastructure of aging synapses in the inferior colliculus (IC), we observed that dense core vesicles (DCVs) were more common in aged tissue. Broadly, DCVs transport and release neuropeptides and neurotrophins in a cell. We sought to determine if DCVs increase in the aging central IC (ICc). We assessed 3-, 19-, 24-, and 28–month-old Fischer Brown Norway (FBN) rats. The tonotopic dorsolateral-ventromedial ICc axis was divided into three regions representing low, middle and high frequencies. We used immunogold transmission electron microscopy to assess DCVs in GABAergic and non-GABAergic neurons by their 1) size, 2) location (boutons/axons, dendrites and somas), and 3) postsynaptic target (soma, dendrites, spines and bouton) when in a presynaptic bouton. Ultrathin sections (~50 nm) were reacted for anti-GABA and stained for contrast. GABAergic synapses were identified as having pleomorphic vesicles, symmetric synaptic junctions, and GABA-positive presynaptic boutons. We analyzed 192,000 μm^2 of tissue.In 3-month non-GABAergic neurons, 55% of DCVs were in a bouton/axon, 44% in dendrites and 1% in somas. In 3-month GABAergic neurons, 65% of DCVs were in a bouton/axon, 32% in dendrites and 3% in somas. ANOVA showed that there

was a significant increase (~170%) of DCVs in non-GABAergic dendrites in the low and middle frequency ICc at 24-months. Significance was not found at 19- or 28-months. Analysis did not reveal significant changes within the GABAergic profiles.Regardless of neurochemical profile, only 2-7% of boutons at 3-months had a DCV. However, despite the age-related loss of non-GABAergic and GABAergic boutons (~20-30%) throughout aging, the number of boutons with at least 1 DCV at 19-, 24-, and 28 months did not decline. At 24- and 28-months there was a noticeable increase (>100%) of non-GABAergic boutons with at least 3 or more DCVs. Thus, the age-related downregulation of boutons may reflect a population that does not release neuropeptides.We conclude, in a model that acquires low frequency presbycusis around ~24-months, age-related increases to neuropeptide/neurotrophin production are prominent in the non-GABAergic dendrites of low/mid frequency ICc at 24-months. As we did not find significant differences between the other age groups, it appears that the increased production and retrograde transport of DCVs occurs within a window of a few months. Perhaps the contents being upregulated at middle-age are aiding in the synaptic rearrangement and pruning of dendrites that occurs in the aging IC. Future studies will need to determine the upregulated neuropeptides/neurotrophins, and if these changes are compensatory or maladaptive.

Disclosures: **A.P. Ohl:** None. **J. Busby:** None. **S.R. Duncan:** None. **L.S. Almassri:** None. **A. Wawrzyniak:** None. **M.C. Iafrate:** None. **D. Albaba:** None. **B. Vega:** None. **E.A. Slabinski:** None. **A.M. Beaver:** None. **A.M. Mafi:** None. **M. Buerke:** None. **J.W. Young:** None. **J.G. Mellott:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.18/E21

Topic: D.05. Auditory & Vestibular Systems

Support: NIH/NIDCD R01 DC017708

Title: Ultrastructure of NPY Profiles in the Young and Old Central Inferior Colliculus

Authors: *L. S. ALMASSRI[1], J. C. HARRIS[1], K. M. CRANE[1], N. J. TOKAR[1], A. P. OHL[1], J. G. MELLOTT[2];
[2]NEOMED, [1]Northeast Ohio Med. Univ., Rootstown, OH

Abstract: The inferior colliculus (IC) exhibits salient age-related changes linked to reduced inhibition, neuronal hyperexcitability, altered hemodynamic responses, and inflammation that are associated with presbycusis. Recent studies have demonstrated that Neuropeptide Y (NPY) is released in a subset of IC GABAergic cells. As GABAergic synapses are reduced in the aged IC, we sought to 1) characterize the ultrastructure of young NPY boutons and 2) determine if NPY synapses are reduced with age. We used 3- and 28–month-old Fischer Brown Norway (FBN) rats. Blocks of tissue were taken from the central IC (ICc). Pre- and/or post-embedding NPY

immuno was conducted for transmission electron microscopy. Ultrathin sections (~50 nm) were stained for contrast. Although our primary interest is in regard to NPY synapses and boutons, we also analyzed astrocytes and endothelial cells for NPY expression.Most (~85%) of young NPY positive boutons/synapses formed symmetric junctions and contained either pleomorphic or round vesicles. The principal target of NPY synapses were NPY-negative dendrites. The size of NPY boutons were commonly between 0.4-0.8 μm^2. NPY positive dendrites were commonly targeted by excitatory synapses. While rare, immunogold labeling detected postsynaptic NPY positive dense core vesicles. In the old tissue, NPY synapses were reduced (20-30%) and observed more frequently on larger dendrites.Immunogold analysis showed a marked decrease of NPY in astrocytes. On average, there were 3-5 gold particles per μm^2 of young astrocyte somas. The average fell to 1-2 particles per μm^2 in old age. Additionally, the number of astrocytic processes that had at least one gold particle was reduced by ~15-20%. Lastly, young endothelial cells were dense for NPY immunogold and also had an age-related loss of NPY expression.We found that most NPY boutons in the IC typically had synapse characteristics of inhibitory ultrastructural (symmetric synapse; flat vesicles) which agrees with recent reports. However, especially in the old tissue, a subset of NPY synapses formed asymmetric/excitatory junctions. Perhaps this change reflects postsynaptic changes unique to neuromodulator/neuropeptide release in old age. Not surprisingly, NPY expression in young astrocytes was robust as NPY is vital for functions related to neurovascular coupling. The age-related loss of NPY in the IC may result in impaired neural input driving hemodynamic responses. Taken together, the age-related loss of NPY in the IC may broadly impair hearing by reducing inhibition and/or affecting neurovascular function.

Disclosures: **L.S. Almassri:** None. **J.C. Harris:** None. **K.M. Crane:** None. **N.J. Tokar:** None. **A.P. Ohl:** None. **J.G. Mellott:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.19/E22

Topic: D.05. Auditory & Vestibular Systems

Support: NIH/NIDCD R01 DC017708

Title: The Aging Ultrastructure of GABAergic Modules in the Inferior Colliculus

Authors: *A. D. WADE[1], E. N. BESKITT[2], A. P. OHL[2], N. J. TOKAR[2], J. G. MELLOTT[3]; [1]Kent State Univ. - Biol. Sci., Kent, OH; [2]Northeast Ohio Med. Univ., Rootstown, OH; [3]Anat. and Neurobio., NEOMED, Rootstown, OH

Abstract: The inferior colliculus (IC) comprises several subdivisions that have unique functional roles. In layer II of the lateral cortex of the IC (IClc) there are modules that densely express GABA and receive somatosensory input. As synapses are lost (~25-30%) in the aging lemniscal

IC, we sought to determine if synapses in the non-lemniscal IClc GABAergic modules are also lost with age. We assessed 3- and 28–month-old Fischer Brown Norway (FBN) rats. We used pre- and post-embedding immuno transmission electron microscopy to identify GABAergic modules and to characterize GABAergic and non-GABAergic synapses based on 1) terminal size, 2) postsynaptic target (dendrite, soma, bouton, and spine), and the presence of dense core vesicles (DCVs). Ultrathin sections (~50 nm) were reacted for anti-GABA immunochemistry and stained for contrast. GABAergic synapses were identified as having pleomorphic vesicles, symmetric synaptic junctions, and GABA-positive presynaptic boutons. We analyzed 958 synapses across 19,200 μm^2: 721 were excitatory, 237 were inhibitory. Of the 237 inhibitory synapses, 174 were classified as GABAergic. The remaining 63 inhibitory synapses were not immunopositive for GAD or GABA. There was a 22% reduction of GABAergic synapses at 28 months; excitatory synapses were reduced by 13%. There was no loss of GABA-negative inhibitory (presumptively glycinergic) synapses at old age. The majority (93%) of young synapses, both types, targeted dendrites. A greater proportion of GABAergic and excitatory synapses were found on larger caliber dendrites in old age. The average area of a young presynaptic GABAergic terminal was 0.73 μm^2 and increased to 0.89 μm^2 with age. The average area of presynaptic excitatory terminals, the density of DCVs, the average inhibitory and excitatory synaptic length and the size of the inhibitory and excitatory vesicle pools did not change from young to old age.Similar to studies in the aging lemniscal IC and layer III IClc, GABAergic synapses were reduced by roughly a quarter and the average terminal area increased. As the range of sizes was unchanged, the larger average area suggests that the lost GABAergic synapses were from smaller boutons. However, unlike our previous report in layer III of IClc (which receives dense excitatory input from auditory cortex), the overall reduction of excitatory synapses in the GABAergic module (which receives dense excitatory input from somatosensory cortex) was markedly reduced, and increases to synaptic lengths, bouton size and the density of DCVs did not occur. Taken together, our data implies that inputs to the IC from non-auditory nuclei may age differently than inputs from auditory nuclei.

Disclosures: **A.D. Wade:** None. **E.N. Beskitt:** None. **A.P. Ohl:** None. **N.J. Tokar:** None. **J.G. Mellott:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.20/E23

Topic: C.01. Brain Wellness and Aging

Support: DFG, German Research Foundation

Title: Unravelling the role of hypothalamic cannabinoid receptor type-1 in systemic ageing

Authors: *M. PALMISANO[1], B. LUTZ[2], A. ZIMMER[1], A. BILKEI-GORZO[1];
[1]Inst. of Mol. Psychiatry, Univ. of Bonn, Med. Fac., Bonn, Germany; [2]Inst. of Physiological Chem., Univ. Med. Ctr. of the Johannes Gutenberg, Univ. Mainz, Mainz, Germany

Abstract: In the hypothalamus, the cannabinoid receptor type-1 (CB1) is highly expressed in the ventromedial nucleus (VMH). Previous studies from our lab showed that constitutive deletion of the CB1 receptor in mice accelerates brain ageing, leading to neuroinflammatory changes with hyperactivation of glial cells, increased release of pro-inflammatory molecules and cognitive decline. Interestingly, these changes were accompanied by age-related histological changes in peripheric organs like skin and testis atrophy as well as osteoporosis. Whether those observed in the peripheric organs of mice were direct consequences of a local deletion of CB1 or an indirect consequence of altered hypothalamic neurohormonal regulation in knockout mice is still not known. Hence, we asked whether deleting or restoring the CB1 receptor in a brain-region-specific manner, specifically in the VMH, can respectively accelerate or prevent mice bodily ageing. We performed stereotaxic injections of rAAV1/2 expressing Cre in 2-month-old CB1 $^{flox/flox}$ animals to delete the CB1 gene (conditional KO) and in CB1-deficient (CB1-STOP) mice to induce its re-expression (conditional rescued). Controls from both strains were injected with the empty vector. Mice were aged to 12 months, and their physical and body conditions were monthly monitored until the age of 17-18 months using the Frailty Index tool. In addition, we examined the body weight, body temperature and locomotor activity in the open field test. Next, we aimed to investigate skin and testis histology by hematoxylin-eosin staining. Neuroinflammatory changes in the VMH were explored by checking glial cell activity by immunostaining. CB1 conditional KO mice did not display any difference in Frailty Index scores compared to the controls. However, they showed decreased body temperature at the age of 12 months and decreased locomotor activity at the age of 14 months. Moreover, they reported enhanced glial cell density and increased microglial production of tumor necrosis factor alpha (TNF-alpha) in VMH as opposed to their age-matched controls. CB1 rescued mice showed improved Frailty Index scores at the age of 13 and 14 months in contrast with the constitutive KO. Unexpectedly, their locomotor activity was markedly reduced at the age of 14 months and no difference in body weight or temperature was found between the two groups. We propose that an intact CB1 receptor signaling in the VMH plays an important role in reducing hypothalamic inflammation, thus influencing neurohormonal regulation and counteracting the propagation of systemic ageing.

Disclosures: **M. Palmisano:** None. **B. Lutz:** None. **A. Zimmer:** None. **A. Bilkei-Gorzo:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.21/E24

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG26158
NIH R01 AG038465

Title: Environmental pollutants are associated with cortical thinning in a lifespan sample

Authors: *C. HABECK[1], V. KALIA[2], Y. LAI[2], Y. GU[3], G. G. MILLER[2], Y. STERN[4]; [2]Envrn. Hlth. Sci., [3]Neurology, Epidemiology, [4]Cognitive Neurosci. Dvision, [1]Columbia Univ., New York, NY

Abstract: In the context of understanding the impact of environmental factors on cognitive function and brain health, our research has focused on assessing chemical exposures and their potential effects on cognitive aging. Through comprehensive analyses of plasma samples using gas chromatography-high resolution mass spectrometry, we have determined the concentrations of 60 common environmental pollutants, including pesticides, industrial chemicals, and other contaminants associated with potential health risks. By quantifying these exposures, known known as part of the “blood exposome," our aim was to help illuminate how environmental pollutants may influence cognitive health and brain function. Our study involved 147 cognitively healthy participants aged 20-80 years old, with both structural-brain imaging data and exposome measurements collected twice, approximately 5 years apart. We examined the longitudinal relationship between blood-concentration changes in exposome substances and cortical thinning in 68 surface brain regions using statistical regression analysis, while controlling for age, sex, years of education, and outcome measure of interest (mean cortical thickness or global cognition) at baseline. FDR corrections for FDR<0.1 were imposed for the 60 x 68 =4,060 regression analyses. Congruent with our prior expectations of mainly negative effects of exposome substances on brain health, we observed 23 negative associations between longitudinal changes in cortical thickness in mainly 3 areas (FreeSurfer labels: lh_rostralanteriorcingulate ,lh_superiorfrontal, rh_insula) and increased exposure in mainly 3 substances: Diethyl-Phthalate (a plasticizer), Mirex (found in pesticides and flame retardants), and Phenacetin (a synthetic analgesic). We found one paradoxical positive association between the change in Etridiazole, a fungicide, and cortical thickness in the right inferior parietal gyrus. When testing these 3 substances for longitudinal associations with global cognition (a composite of episodic memory, fluid reasoning, perceptual speed, and vocabulary), only increased exposure of Mirex showed a negative correlation (p=0.0230), adjusted for age, sex, education, and global cognition at baseline. We supplemented these main analyses with split-sample validations, using a variety of additional tools, and consistently found the blood exposures to contribute predictive utility for both endpoints over and above the covariates. These findings highlight the potential importance of blood-based exposome substances in determining cognitive and brain health.

Disclosures: C. Habeck: None. **V. Kalia:** None. **Y. Lai:** None. **Y. Gu:** None. **G.G. Miller:** None. **Y. Stern:** None.

Poster

PSTR072. Aging in the Brain: Molecular and Structural Changes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.22/E25

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant R01 AG071686-01

Title: Surgical Parabiosis: Complications and solutions in aging mice

Authors: *S. RODRIGUEZ[1], C. M. CARVER[1], A. J. DOSCH[1], D. M. HUFFMAN[6,7], F. D. DUKE BOYNTON[2], K. AYASOUFI[3], M. J. SCHAFER[1,4,5];
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Abstract: Surgical parabiosis can be used to study the mechanistic contributions of the circulating milieu to aging and regenerative processes in the brain and other organs. This powerful model presents diverse complications based on age, strain, sex, and other experimental parameters. In young (Y) and old (O) male and female C57BL6 mice, we optimized heterochronic (n= 12 Y-O) and isochronic (n= 10 Y-Y, n= 7 O-O) parabiosis. Throughout protocol development, we identified several complications including variable responses to anesthesia, external and internal dehiscence, dehydration, and weight loss. We identified and implemented solutions during surgical and post-surgical periods, including titrated anesthesia, reinforced internal sutures, topical agents to promote wound healing, and enhanced supplementation. By adopting protocol changes we increased survival. Separately, we confirmed the time course of chimerism in heterogenic pairs of C57BL6 and Tg(act-EGFP)Y01Osb (eGFP) mice. Baseline and longitudinal blood samples were collected via tail vein nick. Flow cytometry was used to visualize GFP-positive cells from the parabiont blood samples. We found that chimerism occurs as early as five days post-surgery. Finally, we also confirmed that GFP+ cells infiltrate the brains of C57BL6 parabionts in heterogenic pairs through fluorescent imaging. Use of our optimized protocol can foster efficient execution of the surgical parabiosis model to dynamically study mechanisms of aging and regeneration.

Disclosures: S. Rodriguez: None. **C.M. Carver:** None. **A.J. Dosch:** None. **D.M. Huffman:** None. **F.D. Duke Boynton:** None. **K. Ayasoufi:** None. **M.J. Schafer:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.01/E26

Topic:

Support: R21AG059195 to JKB
RF1AG057768 to JKB

RF1AG078299 to JKB
R21AG056901 to TJM

Title: Perinatal choline supplementation prevents epigenetic changes in the hippocampus of the APP^{NL-G-F} Alzheimer's disease model mice

Authors: *T. J. MELLOTT, T. BELLIO, J. LAGUNA-TORRES, J. K. BLUSZTAJN; Pathology, Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Dietary choline is an essential nutrient that plays a crucial role in various physiological processes, including brain development and function. During pregnancy, choline is particularly important for the fetus, as it contributes to brain development. Previous studies have shown that high choline intake by pregnant and nursing mothers, in rodent models, improves cognitive function of the offspring throughout life and that it ameliorates cognitive deficits, as well as brain neuropathologic and transcriptomic abnormalities in Alzheimer's disease (AD) model mice. These actions of choline may be mediated by epigenetic mechanisms. Choline in the diet is a major source of methyl groups which are used for multiple methylation reactions and studies have shown that maternal choline intake during pregnancy can influence DNA- and histone methylation patterns in the developing fetus. We performed transcriptomic analysis (RNA-seq) of hippocampal samples from 3, 6, 9, and 12-month-old C57BL6/J wild type- and APP^{NL-G-F} AD model mice whose mothers consumed either an AIN76A diet containing 1.1 mg/kg of choline chloride (Control) or 5 mg/kg of choline chloride (Supplemented) during pregnancy and lactation. All offspring consumed control diet following weaning. The expression of multiple genes involved in DNA methylation (DNA methyltransferases: *Dnmt1, Dnmt3a, Dnmt3b*) and histone acetylation/deacetylation (*Hat1, Hdac1, Hdac2, Hdac5, Hdac6, Hdac7, Hdac9, Hdac10, Hdac11*) were significantly modified by age. The expression of these genes was also significantly altered in control-diet APP^{NL-G-F} mice compared to control-diet C57BL6/J animals. Moreover, choline supplementation during early development prevented the AD model-induced changes in the expression of these genes as well as number of other genes known to be regulated by DNA methylation (*Bin1, Ddr1, Daxx, Rpa1, Pdgfrb, Crh, Stk32c, Unc5c*) or involved in epigenetic regulation of gene expression *(Sirt3, Sirt6, Sirt7, Kat2a, Mecp2, Mbd3, Mbd5*). Taken together the data show that the hippocampus of the APP^{NL-G-F} mice is characterized by an age-dependent concerted alteration in expression of genes related to epigenomic regulation and that perinatal choline supplementation protects against those changes.

Disclosures: T.J. Mellott: None. **T. Bellio:** None. **J. Laguna-Torres:** None. **J.K. Blusztajn:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.02/E27

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

Support: R21AG059195
RF1AG057768
RF1AG078299
R21AG056901

Title: Perinatal choline supplementation modulates neuroinflammatory processes and ameliorates synaptic deficits in the APP^{NL-G-F}Alzheimer's disease mouse model

Authors: *T. A. BELLIO[1], B. Z. COHEN[2], M. S. CAMPION[2], J. Y. LAGUNA-TORRES[1], J. CHOU[2], S. DEVARAJ[2], J. K. BLUSZTAJN[1], T. J. MELLOTT[1];
[1]Pathology, [2]Boston Univ. Sch. of Med., Boston, MA

Abstract: Multiple animal studies have demonstrated that Alzheimer's disease (AD) model mice that received a diet high in the essential nutrient choline had reduced amyloidosis, cholinergic deficits and gliosis, and increased adult neurogenesis. In this study, we investigated the lifelong effects of perinatal choline supplementation on AD-like neuropathology and inflammation using the APP^{NL-G-F} mouse model of AD. Pregnant and lactating mice were given an AIN76A diet containing either 1.1 g/kg (control) or 5 g/kg (supplemented) of choline chloride until weaning. Subsequently, all offspring received the control diet throughout their life. At 3, 6, 9, or 12 months of age, the right brain hemisphere was used for immunohistochemical analysis of Aβ42, Iba1, and GFAP proteins, while the left hemisphere was used for hippocampal and cerebral cortical RNA sequencing. Qualitative assessments of Iba1 and GFAP immunostaining demonstrated marked inflammation in APP^{NL-G-F} mice compared to wildtype mice. Perinatal choline supplementation reduced this inflammation in 9-month-old APP^{NL-G-F} mice. Furthermore, perinatal choline supplementation significantly altered the overall count and size of Iba1+ microglia near amyloid plaques in APP^{NL-G-F} mice. Bioinformatic analysis of the RNA-sequencing revealed that the most differentially expressed genes in APP^{NL-G-F} mice, as compared to wildtype mice, are related to inflammatory processes, cytokine production, and complement immune system function (*Trem2, Tyrobp, Cd68, Gfap, C3ar1, Itgax, Tlr4)*. Remarkably, in the hippocampus of 12-month-old APP^{NL-G-F} mice, perinatal choline supplementation significantly reduced the levels of transcripts of genes involved in immune response and NF-kappa B signaling (*C1qa, C1qb, C1qc, C1qa, Apoe, Myd88, Ticam1, Plcg2, Tab1, Nfkb1, Nfkb2, Rela*). In APP^{NL-G-F} mice, choline supplementation also significantly increased the expression of genes involved in cyclic nucleotide signaling (*Adcyap1, Gucy1a1, Gucy2e*), nucleotide processing and recycling (*Cmpk1, Hprt1)* and bioenergetics (*ATP8, ND3, Ndufb5, Cox16, Atp5g3)*. The APP^{NL-G-F} genotype, as compared to wildtype mice, led to severe deficits in the expression of genes regulating synaptic and neuronal functioning (*Gad1, Dlg4, Snap25, Syt1, Syn1, Gabra1, Vamp2, Pak1)* and perinatal choline supplementation ameliorated some of them. These results suggest that perinatal choline supplementation reduces AD-like neuropathology by modulating the expression of genes involved in neuroinflammatory responses, energy homeostasis, and synaptic functioning.

Disclosures: T.A. Bellio: None. **B.Z. Cohen:** None. **M.S. Campion:** None. **J.Y. Laguna-Torres:** None. **J. Chou:** None. **S. Devaraj:** None. **J.K. Blusztajn:** None. **T.J. Mellott:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.03/E28

Topic:

Support: Lisa Dean Moseley Foundation Grant 2019-2023
NIH Grant 1DP2EB028110-01

Title: Non-viral Reprogramming-based Vasculogenic and Neurogenic Cell therapies Drive Improved Memory and Reduced Neuropathological Burden in a Mouse Model of Alzheimer's Disease

Authors: *D. F. ALZATE-CORREA[1], J. STRANAN[1], M. A. RINCON BENAVIDES[1,2], W. LAWRENCE[1,3], N. HIGUITA CASTRO[1,4], D. GALLEGO PEREZ[1,4];
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Abstract: Alzheimer's Disease (AD) is characterized by a progressive cognitive decline, loss of synaptic connections and neurons, and the formation of amyloid plaques and neurofibrillary tangles lesions. Numerous studies indicate a correlation between cerebrovascular impairment and the development of AD. These r alterations precede the formation of amyloid plaques, tangles, and the onset of cognitive decline, suggesting that impaired cerebrovascular function plays a key role in the onset AD neuropathology. In consequence, therapeutic interventions aiming to restore cerebrovascular function may constitute crucial strategies to attenuate the progression of the disease. To implement safe and efficient cell therapies in AD, we used electroporation, to deliver 3 pro-vasculogenic and 3 pro-neurogenic*)* transcription factors to reprogram fibroblasts (pMEFs) into induced endothelial cells (iECs) and induced neurons (iN) respectively. To evaluate vasculogenic therapeutic potential, pMEFs labeled with 5-bromo-2'-deoxyuridine (BrdU) and transfected with *Etv2, Foxc2, Fli1 (EFF)* or a control empty plasmid were delivered with 3 intracranial injections into the lateral ventricles (LV) of females from the triple transgenic murine model of AD (3xTg-AD) or Wild-Type Controls. Within each cage mice with the same genotype were randomly assigned to either vasculogenic, or control cell injections. Two weeks after the last injection spatial memory was analyzed with the Barnes Maze. Similarly, pMEFs labeled with BrdU and transfected with the neurogenic factors *Ascl1, Brn2, Myt1l (ABM)* or an empty plasmid were injected into the hippocampus of 3xTg-AD or Wild-Type Controls females. Four weeks after the injection spatial and recognition memory was analyzed. All the analysis were conducted by and experimenter blinded to the cell treatment. Our results indicate that pMEFs pre-programmed into iECs induce reduction of the spatial memory deficits together with an increase in global cerebral blood flow (CBF). Histological analysis also show that our injected cells can survive for at least 4 weeks inside the brain and induce an increase in the total vascular area. Also, Injection of *EFF*-transfected cells seems to induce the activation of resident microglia cells together with a reduction in amyloid-beta load. On the other hand, pMEFs pre-programmed into iNs can survive for at least 6 weeks and express markers of mature neurons inside the brain parenchyma and induce a reduction of amyloid-beta levels. Together our results indicate that the

development of electroporation-based cell therapies by direct reprogramming constitute a promising approach to treat AD and AD-related dementias.

Disclosures: D.F. Alzate-Correa: None. **J. Stranan:** None. **M.A. Rincon Benavides:** None. **W. Lawrence:** None. **N. Higuita Castro:** None. **D. Gallego Perez:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.04/E29

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

Support: HELSE SøR-ØST 2020-2024.05.31

Title: Nad^+ normalizes circadian rhythm and improves memory in alzheimer disease animal models

Authors: *S. ZHANG[1], M. LAGARTOS[2], S. LAUTRUP[2], E. FANG[2,3];
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Abstract: Abnormal circadian rhythm is a common feature and risk factor of Alzheimer's disease (AD), and it occurs much earlier than memory impairment. The underlying mechanisms of circadian derailment in AD are poorly understood and whether circadian disorder can be targeted for therapeutic intervention has not yet been determined. Studies from our lab and others show reduced NAD^+ in AD, and that NAD^+ supplementation inhibits AD pathologies and normalizes 'clock genes' to that of wild type in AD *C.elegans*. Here, we hypothesize that NAD^+ upregulation could normalize circadian rhythm in AD, leading to neuronal resilience and memory retention. For this project, we have applied a cross-species approach, comprising *C. elegans* and mice, as well as human blood samples. Our results show that in AD, the transcriptional profiles of genes associated with the circadian rhythm were abnormal, while NAD^+ supplementation inhibited AD pathologies, at least partially, via the normalization of key circadian-related genes. Meanwhile, the normalization of key circadian-related genes can activate mitophagy in both basal and mitochondrial stress conditions, bringing further healthspan benefits to AD *C.elegans* models. As the brain 'garbage clearance system' mitophagy/autophagy is impaired in AD. Our study links two AD risk factors, compromised mitophagy/autophagy and circadian derailment, pointing to novel therapeutics against AD.

Disclosures: S. Zhang: None. **M. Lagartos:** None. **S. Lautrup:** None. **E. Fang:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.05/E30

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

Support: Region Occitanie (Toulouse, France)
SATT AxLR (Montpellier, France)

Title: The alkaloid MED0092 is a potent sigma-1 receptor positive modulator with cognitive and neuroprotective properties

Authors: *L. CROUZIER[1], J. MEUNIER[1], A. CARLES[1], A. MORILLEAU[1], C. VRIGNEAU[1], M. SCHMITT[3], J.-J. BOURGUIGNON[3], B. DELPRAT[1], T. MAURICE[1], *L. CROUZIER[2];
[2]MMDN, Univ. Montpellier, EPHE, INSERM, Montpellier, Cedex 5, [1]INSERM UMR-S1198, Montpellier, France; [3]LIT, Univ. Strasbourg, CNRS, Strasbourg, France

Abstract: By using an *in vivo* phenotypic screening assay in zebrafish, we identified MED0092, an alkaloid, as a positive modulator of the sigma-1 receptor (S1R). The *wfs1ab*^{KO} zebrafish larva, a model of Wolfram syndrome, is hyperactive in the visual motor response as compared to *wfs1ab*^{WT} control larva. This hyperlocomotion is a consequence of impaired communication between the endoplasmic reticulum and mitochondria, at contacts points termed MAMs, and this deficit is a consequence of the mutation affecting Wolframin protein. We previously reported that ligand activating S1R, another MAM protein, restored the cellular and behavioral deficits in patient fibroblasts and zebrafish and mouse models. We therefore screened a library of 108 repositionable and natural compounds in zebrafish. One hit restored normal mobility in *wfs1ab*^{KO} larvae without affecting *wfs1ab*^{WT} controls, the alkaloid MED0092. The drug did not bind S1R (but S2R with low affinity), nor dissociated S1R from BiP (a S1R activity assay *in vitro*), but shifted the IC_{50} of the reference agonist PRE-084 to lower values, therefore showing S1R positive modulation not agonism. MED0092 restored learning ability in *Wfs1*$^{\Delta Exon8}$ mice, in Dizocilpine-treated mice and in $A\beta_{25\text{-}35}$-treated mice, thus behaving *in vivo* as a S1R agonist, as expected for S1R positive modulators. The effects were observed at low intraperitoneal doses (~1 mg/Kg), not shared by dMED0092, the desmethyl metabolite of MED0092, and blocked by the S1R antagonist NE-100. These data identified the pharmacological action of MED0092. They showed that the alkaloid is as active as reference pharmacological drugs in memory and neuroprotection with potential impacts in rare genetic diseases (e.g., Wolfram syndrome) and neurodegenerative pathologies (e.g., Alzheimer's disease), as expected for S1R positive modulators.

Disclosures: **L. Crouzier:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **J. Meunier:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **A. Carles:** None. **A. Morilleau:** None. **C. Vrigneau:** None. **M. Schmitt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **J. Bourguignon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **B.**

Delprat: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **T. Maurice:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **L. Crouzier:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.06/E31

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

Title: Long-term treatment with Citalopram restores cognitive function and reduces amyloid-beta pathology in two mouse models of Alzheimer's disease

Authors: C. BOUTER[1], F. SPANDAU[1], S. F. BOCK[1], S. E. CHINA[1], T. A. BAYER[1], L. M. J. TRENDELENBURG[1], N. BEINDORFF[2], J. WILTFANG[1], ***Y. BOUTER**[1];
[1]Univ. Med. Göttingen, Goettingen, Germany; [2]Berlin Exptl. Radionuclide Imaging Center, Charite, Berlin, Berlin, Germany

Abstract: Introduction: Limited therapeutic effects of current Alzheimer (AD) treatments highlight the need for new research approaches. Drug repurposing can enhance traditional drug development and could accelerate the development of new treatments for patients with AD and mild cognitive impairment. Previous studies have shown that long-term use of selective serotonin reuptake inhibitors (SSRIs) can delay the progression from mild cognitive impairment to AD by several years in patients with a history of depression (Bartels et al., 2018). In addition, we have recently demonstrated an inverse correlation between the duration of SSRI treatment and amyloid burden in both cognitively normal and cognitively impaired patients (Bouter and Bouter, 2022). Therefore, the objective of the present study was to investigate the effects of prolonged Citalopram treatment on behavioral deficits and Abeta pathology in two different AD mouse models.**Material and Methods:** 10-week-old 5XFAD and Tg4-42 AD mice were treated daily with 10 mg/kg Citalopram for 6 months. At the end of the treatment period, behavior tests (n=12-15) were performed assessing memory, motor functions and anxiety (Rotarod, Novel Object Recognition, Elevated-Plus-Maze, Dark/Light & Morris Water Maze). Abeta levels in the blood plasma were measured using the MSD® 6E10 Abeta Triplex Assay, whereas Abeta load in the brain was evaluated immunohistochemically (n=7-8). ^{18}F-FDG-PET was used to analyze the cerebral glucose metabolism after Citalopram treatment (n=5-6). **Results and Discussion:** Long-term-treatment with Citalopram normalized the anxiety behavior and locomotor activity in 5XFAD mice. Additionally, Citalopram improved recognition and working memory of 5XFAD and Tg4-42 mice. Citalopram significantly decreased the concentration of Aβ40 and Aβ42 in the blood plasma of 5XFAD and Tg4-42 mice, respectively. Furthermore, long-term treatment with Citalopram significant reduced the plaque size in 5XFAD mice. In addition, Citalopram treatment restored brain glucose metabolism in AD mice. In conclusion, the present study shows that Citalopram treatment can be beneficial for several altered parameters in AD including motor

deficits, anxiety and memory as well as Abeta pathology in two different AD models. Our findings support the potential use of SSRI-based medications as a therapy for AD.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.07/E32

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

Support: Provincial Key Innovation Program 2019JZZY020909
Natural Science Foundation of China 82274407
CAMS Innovation Fund for Medical Science 2021-I2M-1-071

Title: Perk pathway inhibition alleviated neurocognitive decline in chronic intermittent hypoxia accelerated alzheimer's disease developments

Authors: *L. DU[1], Y. LI[1], Z. WANG[2], X. WANG[1], Y. HAN[1], C. WANG[1];
[1]Inst. of Mol. Med. & Innovative Pharmaceutics, Qingdao Univ., Qingdao, China; [2]Binzhou Med. Col., Binzhou, China

Abstract: PERK pathway inhibition alleviated neurocognitive decline in chronic intermittent hypoxia aggravated Alzheimer's Disease
Lida Du[1], Yu Li[1], Ziming Wang[2], Xuan Wang[1],Yantao Han*[1], Chunbo Wang*[1]*1. Institute of Molecular Medicine & Innovative Pharmaceutics, Qingdao University2. Binzhou Medical College*
Abstract Alzheimer's disease (AD) is a major neurodegenerative disease that is associated with progressive cognitive decline. AD commonly co-exists with obstructive sleep apnea (OSA) in the elderly. Chronic intermittent hypoxia (CIH) is an OSA-associated pathological condition that results in cognitive impairments. Activation of the PERK pathway exacerbates endoplasmic reticulum (ER) stress induced by CIH in various brain areas, thereby exacerbating the progression of AD. However, the underlying relationship between the upregulation of PERK activity due to sleep apnea and the development of AD remains elusive. In this study, we investigated the long-term effects of CIH treatment on a chronic transgenic animal model of progressive Alzheimer's disease. We explored the pharmacological effects of inhibiting the PERK pathway in mitigating memory decline during the co-occurrence of CIH and early-stage AD. Mice that underwent CIH treatment showed a significant acceleration in early AD progression. We observed that PERK pathway inhibition attenuated the aggravating effects of CIH on AD progression. Inhibition PERK ameliorated CIH-accelerated AD cognitive and synaptic plasticity impairments. Our findings also elucidated the pharmacological effects of

PERK inhibitors on CIH-aggravated memory decline in developing AD. Our study sheds light on the potential pharmacological targets for ameliorating cognitive disorders that arise in OSA patients combining early AD.

Disclosures: **L. Du:** A. Employment/Salary (full or part-time):; Qingdao 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.; Yikang Pharmaceutical Co, Ltd. **Y. Li:** None. **Z. Wang:** None. **X. Wang:** None. **Y. Han:** A. Employment/Salary (full or part-time):; Qingdao University. **C. Wang:** A. Employment/Salary (full or part-time):; Qingdao University.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.08/E33

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

Title: Evaluating MSUT2 inhibition by repurposed drugs in PS19 tauopathy mice

Authors: ***N. E. HENDRICKS**[1,2], P. J. MCMILLAN[2,3], R. L. UHRICH[2], J. D. BAKER[2], J. M. WHEELER[1,2], B. C. KRAEMER[4,2,5,3];
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder, with the hallmark pathology being neurofibrillary tangles (NFTs) composed of tau and Amyloid Beta (Aβ) plaques. We previously identified a gene called MSUT2, the mammalian homolog of the *C. elegans* gene *sut-2*, or *su*ppressor-of-*t*au 2. Previous studies have shown that loss of *sut-2* in *C. elegans* or *Msut2* in mice resulted in decreased tau accumulation and protected against AD neurodegeneration (PMID: 31852801). The primary activity of MSUT2 appears to be binding to poly(A) RNA. We previously conducted drug repurposing screens and identified and published several candidates that inhibit MSUT2 RNA binding activity (PMID: 32981422, 32589834). In a more recent screen of the Broad Drug repurposing library, we found a series of proton pump inhibitors (PPIs) also exhibited low micromolar IC50 inhibition of MSUT2. PPIs are widely used to treat heartburn and other symptoms caused by excessive gastric acid. Among the PPIs identified we selected omeprazole as a promising drug repurposing candidate because it crosses the blood brain barrier, inhibits MSUT2 poly(A) function with reasonable selectivity, is non-toxic, and is already an FDA approved drug. To pilot small molecule inhibition of MSUT2 *in vivo,* we evaluated the consequences of omeprazole treatment in PS19 tau transgenic mice. In previous work we showed PS19 mice with the MSUT2 gene knocked out exhibited reduced tau neuropathology and improved learning and cognition compared to normal PS19 mice. To test

omeprazole, we conducted a blinded study using PS19 transgenic and non-transgenic littermate mice (n = 40 PS19, 23 non-Tg). At 6.5 months of age, mice were given Omeprazole chow (1500 mg/kg) or regular chow (PicoLab Diet 5058) for 8 weeks, with weekly weight and limb clasping scores collected. Barnes maze testing was conducted at 8 - 8.5 months of age. We found that there was a genotypic difference between the PS19 and non-Tg groups, with non-Tg mice performing significantly better on Barnes training and probe location compared to the PS19 mice. We did not see a significant difference in treatment groups between genotypes. However, in evaluating pathological tau burden in the treated and untreated PS19 mice we observed no changes in pTau (AT180), variable neuronal loss, and negligible NFTs. The diminished neuropathology changes in this cohort of PS19 make conclusive determination of PPI effectiveness against tauopathy *in vivo* challenging. To address the shortcomings of the pilot study, we are now working with a re-derived PS19 strain exhibiting demonstrably robust tau neuropathology and plan to test novel MSUT2 inhibitors in this refreshed PS19 line in the future.

Disclosures: N.E. Hendricks: None. **P.J. McMillan:** None. **R.L. Uhrich:** None. **J.D. Baker:** None. **J.M. Wheeler:** None. **B.C. Kraemer:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.09/E34

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

Title: Antisense oligonucleotide-mediated upregulation of Na$_V$1.1 decreases seizures and increases gamma power in APP/PS1 and Tg4510 mouse models of Alzheimer's Disease

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Abstract: Alzheimer’s disease (AD) is the most common cause of dementia, and epilepsy is frequently associated with AD. Seizures in patients with AD are typically non-convulsive and difficult to diagnose, however subclinical epileptiform discharges are observed in >50% of patients and epilepsy in AD is associated with more rapid cognitive decline (Csernus et al 2022).It was shown previously that Na$_V$1.1 overexpressing interneuron transplants restored gamma oscillatory activity and reduced epileptiform discharges in an AD mouse model (Martinez-Losa et al 2018). Here we use the Targeted Augmentation of Nuclear Gene Output (TANGO) antisense oligonucleotide (ASO-84) to increase the endogenous expression of Na$_V$1.1 protein in neurons in two different AD mouse models and then assessed seizure frequency and gamma activity, an indicator for cognitive function. The TANGO approach has been shown to reduce seizures in patients with Dravet syndrome and a Dravet mouse model. ASO-84 reduces inclusion of a non-productive, alternatively spliced exon in the *SCN1A* gene to increase productive *SCN1A* mRNA and Na$_V$1.1 protein. ASO-84 was administered via intracerebroventricular injection to AD mice (rTg4510 and APP/PS1) at 3 months of age.

Surface electrodes were implanted on frontal and parietal cortex, and an indwelling electrode was implanted in hippocampus 1 month post injection, and 24hr electroencephalography (EEG) recordings was performed 5 months after ASO injection. Brain tissues were collected after the last EEG recording to confirm ASO exposure using LCMS as well as Nav1.1 upregulation using Meso Scale Discovery (MSD.) ASO-84 significantly upregulated Nav1.1 protein in hippocampus and cortex for 5 months after a single injection. Both AD mouse models demonstrated many electrographic seizures when quantified during a 3hr period during their active cycle. Both animal models treated with ASO-84 had a significant reduction in seizures and showed an increase in low gamma power in all three brain regions compared to vehicle-treated controls. Taken together, these results suggest that an ASO that increases Nav1.1 expression in brain may reduce seizures and positively influence electrographic measures in AD mice. This provides additional evidence for targeting Nav1.1 as a potential therapeutic approach for AD patients with epilepsy.

Disclosures: **S. Ji:** A. Employment/Salary (full or part-time):; Stoke Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stoke Therapeutics. **Z. Han:** A. Employment/Salary (full or part-time):; Stoke Therapeutics. **M. Catron:** A. Employment/Salary (full or part-time):; Pyschogenics. 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.; Stoke Therapeutics. **Y. Cui:** A. Employment/Salary (full or part-time):; Stoke Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stoke Therapeutics. **A. Christiansen:** A. Employment/Salary (full or part-time):; Stoke Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stoke Therapeutics.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.10/E35

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

Title: Transferrin receptor binding BBB-shuttle facilitates brain delivery of a therapeutic Aβ-antibody: A mouse whole-brain 3D light sheet imaging study

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Abstract: Amyloid β (Aβ)-directed antibodies (aducanumab, lecanemab) have recently been approved for the treatment of early-stage Alzheimer’s disease (AD). However, these compounds show only modest efficacy and adverse effects are common, such as brain swelling and

intracerebral haemorrhage, which currently limits the use of Aβ antibodies in the clinic. Improved CNS access of Aβ-directed antibodies may potentially increase therapeutic benefits while also reducing adverse effects. Using a high-throughput light sheet fluorescence microscopy (LSFM) pipeline, the present study aimed to 3D map and quantify whole-brain distribution of a blood-brain barrier (BBB) shuttle-enhanced Aβ antibody in a transgenic mouse model of AD. 7-11 month-old double transgenic mice expressing mutant forms of human APP and PSEN1 (ARTE10 mice) received a single infusion (50 nmol/kg, i.v.) of aducanumab biosimilar (AduBS; n=6), aducanumab biosimilar combined with anti-mouse transferrin receptor (mTfR) BBB-shuttle (AduBS-BBB; n=6), or control hIgG (Contr; n=4). Mice were terminated 48 after the infusion. Other ARTE10 mice were administered (10 or 50 nmol/kg, i.p.) AduBS (n=8), AduBS-BBB (n=10), or Contr (50 nmol/kg, n=10) once weekly for 12 weeks. Intact brains or hemispheres were stained with an antibody against hIgG, cleared and scanned on a LSFM. Deep-learning computational analysis was applied for automated whole-brain anatomical mapping and quantification of IgG distribution using a custom mouse brain atlas. Whereas AduBS showed virtually no brain exposure following acute administration in ARTE10 mice, AduBS-BBB distributed to brain areas with severe Aβ plaque load, notably the cerebral cortex. When using a chronic dosing regimen, both antibodies accumulated in brain areas with high Aβ plaque load. Compared to AduBS, a similar brain distribution pattern was achieved using a five times lower dose of AduBS-BBB. In conclusion, using TfR binding BBB-shuttle facilitates brain delivery of a therapeutic Aβ antibody in transgenic AD mice. Quantitative 3D LSFM imaging is highly instrumental to visualize, map and quantify distribution of therapeutic antibodies in the intact mouse brain at micrometre resolution.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.11/E36

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

Support: Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) Grant FI-B-00378
María de Maeztu Unit of Excellence Grant MDM-2017-0729
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Title: Protein RTP801 regulates the activity of the tRNA splicing ligase complex

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Abstract: Background: RTP801/REDD1 is a stress responsive protein overexpressed in neurons of patients with neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases. The main described function of RTP801 is to regulate the mTOR/Akt pathway, although we recently showed that it also participates in neuroinflammation and the regulation of neuronal plasticity via extracellular vesicles. In preliminary proteomic studies from our laboratory, RTP801 was found to interact with HSPC117 and DDX1, two proteins of the *tRNA splicing ligase complex*, which performs the ligation of the tRNA fragments formed during splicing. This complex also mediates the splicing of *XBP1* mRNA, a transcription factor and an effector of the unfolded protein response. Aims: Since alterations in tRNA metabolism have recently been associated to the development of some neurodegenerative diseases, we aimed to deeper study the relationship between RTP801 and these tRNA-processing enzymes. Methods: We immunoprecipitated RTP801 in DSP-treated HEK293 cells to study its interactors. RTP801, DDX1, HSPC117 or a combination of them were silenced in HEK293 cells and rat primary cortical neurons. After that, we evaluated the stability and the expression levels of the members of the *tRNA splicing ligase complex* by western blotting and qPCR, respectively. The splicing of XBP1 was used as a readout of the complex mRNA ligase activity. tRNAs signature was assessed by Hydro-tRNA sequencing; briefly, RTP801 was silenced in the hippocampi of 6-month-old wild-type or 5xFAD male mice, small RNAs (<200 nt) were isolated with Zymo-Spin columns, and tRNAs (50-100 nt) were isolated by agarose gel electrophoresis and sequenced. Results: We confirmed by immunoprecipitation that endogenous RTP801 interacts with the *tRNA splicing ligase complex*, specifically with DDX1, HSPC117 and CGI-99. HSPC117 appears as the key regulator of the complex stability and activity. On the other hand, RTP801 does not affect the stability of the complex neither in neurons nor HEK293 cells, but strikingly, it inhibits its mRNA ligase activity. Finally, we found differences between wild-type and 5xFAD mice in hippocampal tRNAs signature, and silencing neuronal hippocampal RTP801 mildly affected this tRNA pool. Conclusions: We propose RTP801 as a novel member of the *tRNA splicing ligase complex* and a regulator of its mRNA and tRNA ligase activity. We show that the gene expression and protein stability of RTP801 is tightly regulated by the other members of the complex. We hypothesize that RTP801 binds transiently to the complex and inhibits it, affecting translation by regulating the pool of mature tRNAs.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.12/E37

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

Support: NIH Grant R01AG057555
DSRG, Biochemistry Program, Graduate Center CUNY

Title: Agomelatine, a melatonin receptor agonist and serotonin receptor antagonist, improves cognition in a transgenic rat model of Alzheimer's Disease

Authors: *G. TERRY[1,5], M. MERAV[2], P. ROCKWELL[2], P. SERRANO[3], L. XIE[4], M. FIGUEIREDO-PEREIRA[2];
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Abstract: Alzheimer's Disease (AD) is the most common neurodegenerative disease in humans. Currently, there are limited treatments for AD emphasizing the need to explore novel drug targets for AD. Our lab identified agomelatine (AGO) through a high-throughput drug screening algorithm that identifies possible treatments for AD by analyzing off-target effects of FDA approved pharmaceuticals. AGO, also under the brand name Valdoxan, is used to treat clinical depression. It has potential to treat AD due to its MT1/MT2 melatonin receptors agonistic action coupled to its $5HT_{2C}$ serotonin receptor antagonistic action. This synergistic mechanism of action of AGO could benefit AD as it is a multifactorial disease. To test the efficacy of AGO we used the Fisher transgenic 344-AD rat model of AD, which expresses human mutant "Swedish" amyloid-precursor protein (APPsw) and a Δ exon 9 presenilin 1 (PS1ΔE9). TgF-344AD (Tg) rats exhibit age-dependent progressive AD pathology more closely than other model systems. Male and female TgF344-AD and their wild type littermates were included in our studies. Oral treatment with AGO (dose ~10 mg/kg/day), started at 5 months of age (pre-pathology) and continued for 6 months until the endpoint at 11 months of age. The effect of AGO on cognitive decline was assessed using the hippocampal-dependent active place avoidance task at 9 and 11 months of age. At 11 months of age, transgenic rats have a reduction in cognitive performance compared to their wildtype littermates AGO treated Tg female rats showed a rescue of cognition compared to non-treated Tg female rats. Immunohistochemical analysis confirms the presence of amyloid beta plaque formation in the hippocampus of non-treated transgenic rats and additional studies are being carried out to correlate the rescue in cognition with a reduction in amyloid-beta plaque pathology. We also analyzed the levels of SOX-2, a transcription factor postulated to regulate some AD relevant genes, such as alpha secretase. We found that SOX-2 levels were lower in Tg than WT rats, and AGO-treatment partially reversed the SOX-2 decrease observed in the Tg rats. This rescue effect on SOX-2 levels suggests a potential mechanism for AGO to alleviate amyloid-beta plaque burden in the Tg-treated rats, by increasing non-amyloidogenic processing of APP by alpha-secretase. Based on our data, we propose that AGO, through its role as both an MT1/MT2 agonist and $5\text{-}HT_{2c}$ antagonist, is a drug that can be repurposed to treat AD.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.13/E38

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

Support: Alzheimer's Research UK Grant ARUK-2021DDI-UCL
ADDF-HARRINGTON SCHOLAR PROGRAM

Title: Wnt pathway restoration at the brain neurovascular unit through inhibition of Notum in the APPPS1 mouse model of amyloid pathology

Authors: *S. BENVEGNU[1], S. JOLLY[1], N. J. WILLIS[1], P. SALINAS[1], J. VINCENT[2], Y. JONES[3], M. BICTASH[1], P. V. FISH[1], P. WHITING[1], F. RANDALL[1];
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Abstract: ***Motivation/problem statement:*** Alzheimer's disease (AD) is a progressive neurodegenerative disease. No therapy has been found to alter its progression. Increasing evidence points to a deterioration of the blood brain barrier (BBB) and to the dysfunctionality of the neurovascular unit (NVU) as key components in AD. Wnt pathway regulates multiple cellular processes. Importantly, it maintains neurovascular functions, and evidence indicates Wnt pathway downregulation in AD. Carboxylesterase Notum is a secreted enzyme that inhibits Wnt signalling. Notum is increased in mouse models of AD and in AD patients, and is uniquely expressed in brain endothelial cells. Hence, inhibition of excessive Notum may help to restore the Wnt pathway and maintain a healthy NVU. ***Methods/ approach***: We tested our novel, CNS-penetrant, potent Notum inhibitor, ARUK3001185 in the APPPS1 (B6;C3-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax, Jackson strain 004462) mouse model of amyloid pathology and age-matched wild-type controls to evaluate effects of restoring NVU Wnt signalling via Notum inhibition. We studied the pharmacodynamic and pharmacokinetic profile of ARUK3001185 using immunohistochemistry and gene expression profiling to look at molecular changes in markers of Wnt signalling and also well described pathology in the APPPS1 mouse model. ***Results***: We confirmed *in vitro* that ARUK3001185 is highly selective for Notum by screening against serine hydrolases, kinases, and a panel of other drug targets. We confirmed good brain penetration in pharmacokinetic studies and confirmed it is well tolerated *in vivo*. In cortical microvessels, chronic treatment with ARUK3001185 altered expression of hundreds of genes previously associated with Wnt activation using a combination of RNAseq and the Nanostring NVU-targeted digital spatial profiling. We dosed 9m animals for 5 weeks and then took tissue to study the effects of Notum inhibition of neurovascular markers, amyloid pathology, inflammation and Wnt signalling markers. ***Conclusion/implications***: ARUK3001185 is a potent, selective and CNS penetrant inhibitor of Notum. Oral administration of ARUK3001185 in mouse changed the transcriptomic and proteomic profile of NVU-related cell types, while sparing total tissue changes. ARUK3001185 has been delivered to AD mouse

models to identify potential therapeutic effects. We will present the effects of Notum inhibition on blood brain barrier proteins (Claudin-5), functional vasculature (fibrinogen extravasation), and pathological changes including levels of β-Amyloid, Gliosis (GFAP+/Iba1+ staining) and synapse and neuronal number in the APPPS1 mouse model.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.14/E39

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

Support: I01 BX004730
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RF1AG063913

Title: Effect of the ROCK inhibitor fasudil on the brain tau pathology and proteomic profile in the tau transgenic mouse model of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) represents a major cause of disability for more than 47 million people world-wide. Limited pharmacological approaches to treat cognitive symptoms or to delay clinical decline are currently available and approved by the US Food and Drug Administration (FDA).The purpose of this study is to explore the pharmacological potential of the amyloid-reducing vasodilator fasudil, a selective Ras homolog (Rho)-associated kinase (ROCK) inhibitor, in the P301S tau transgenic mouse model (Line PS19) of neurodegenerative tauopathy and AD. We explored the efficacy of fasudil on the brain tau pathology in 6 months old transgenic mice with already established neuropathology. Using LC-MS/MS and ELISA technologies, we examined the effect of fasudil on tau phosphorylation (pTau), proteomic profile and potential toxicity after daily administration for a period of two weeks.We observed a dose dependent increase in the brain levels of fasudil and its active metabolite hydroxyfasudil in PS19 mice administered with the lower (30 mg/kg) and higher (100 mg/kg) dose of fasudil. Treatment with fasudil significantly affected pTau levels in the brain of PS19 mice. Drug exposure and

efficacy analysis of individual animals revealed a significant negative correlation between the brain levels of pTau-396 and both fasudil ($P<0.05$) and hydroxyfasudil ($P<0.05$). Bioinformatic analysis of proteomic profiles generated a panel of proteins showing significant response to treatment and identified two main networks of core proteins responding to only one dose or showing opposite regulation between low and high doses. Pathway analysis identified metabolic and neurodegenerative-related pathways (R-MMU-1430728 and mmu05022) as the top most represented pathways (FDR<0.0001). Further investigation for different metabolism reactions and sub-systems revealed enrichment for the pathway of the citrate cycle (TCA cycle, hsa00020) (FDR<0.0001). Impaired TCA cycle metabolism, whose reduced products affect mitochondrial function, is associated with tau pathology in aging and multiple neurodegenerative diseases. The treatment with fasudil up-regulated mitochondria/TCA cycle proteins (e.g., Mtco2, Cox7a2, Ndufa4, Ndufs3, Map1lc3a, Map1lc3b, Sdhb, Sucla2) while reducing pTau in the brain of our PS19 mice. Our study expands the current knowledge on the potential use of fasudil for the treatment of certain tauopathies and AD conditions by reducing tau phosphorylation and improving mitochondrial function. Further studies aiming at investigating the mechanism of action of fasudil at early stages of tau-related neuropathology development are needed.

Disclosures: **R. Collu:** None. **Z. Yin:** None. **E. Giunti:** None. **S. Daley:** None. **M. Chen:** None. **P.J. Morin:** None. **R. Killick:** None. **S.T.C. Wong:** None. **W. Xia:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.15/E40

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

Support: NIH Grant R21 AG077694

Title: Effects of aromatase inhibition on hippocampal cellular excitability in the APP/PS1 mouse model of Alzheimer’s disease

Authors: A. R. FRENCH, *C. CHRISTIAN-HINMAN;
Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: Patients with Alzheimer’s disease are at a five-to-ten times greater risk of developing seizures than their peers. The hippocampus is an important focal point in Alzheimer’s disease, where hippocampal degradation contributes to memory loss, and is a common site of seizure initiation in multiple forms of epilepsy. In this context, estradiol, the primary estrogen in the brain, has both positive and negative effects, as it is generally both pro-cognitive and pro-convulsive. In both males and females, neurons in several brain regions, including the hippocampus, express the enzyme aromatase, which converts testosterone to estradiol. Previous studies suggest that aromatase inhibition can modulate hippocampal function and excitability. However, the contribution of neuroestradiol synthesis to hippocampal excitability in the context

of Alzheimer's disease is not known. In this study, we tested whether inhibition of aromatase impacts hippocampal excitability in the APP/PS1 mouse model of Alzheimer's disease, which is prone to hyperexcitability and seizures. APP/PS1 mice (APP) and wild-type (WT) littermates at 11-14 weeks old were injected daily for 7 days with the aromatase inhibitor letrozole (LET, 10 mg/kg i.p.) or vehicle (veh). 24 h after the final injection, acute slices through the dorsal hippocampus were prepared and the response function of CA1 pyramidal neurons to injected current was measured using whole-cell patch-clamp electrophysiology. In males, the rheobase showed a significant interaction between LET treatment and genotype ($F(1,34) = 8.15$, $p = 0.0073$), with initial analyses indicating trends for LET treatment decreasing rheobase in WT mice but increasing it in APP mice (n cells, n mice: WT-veh, 9, 4; WT-LET, 11, 5; APP-veh, 6, 3; APP-LET, 12, 4). These data may therefore suggest that in WT males, basal aromatase activity decreases excitability, but in APP mice this relationship is reversed, such that basal aromatase activity promotes elevated excitability. To see whether the effect of LET was similar in females, we also measured these responses in ovariectomized (OVX) females to isolate the effects to neuroestradiol. Surprisingly, this interaction was not seen in OVX females ($F(1,31) = 0.03$, $p = 0.85$), and neither LET nor genotype had an effect (n cells, n mice: WT-veh, 13, 6; WT-LET, 9, 3; APP-veh, 5, 2; APP-LET, 8, 4). These results suggest that inhibiting aromatase activity may be an effective treatment option for decreasing seizure susceptibility in males with Alzheimer's disease, but not females. Ongoing studies are examining ovary-intact females to determine how the presence or absence of ovarian hormones influences these sex differences.

Disclosures: A.R. French: None. **C. Christian-Hinman:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

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

Support: R01 AG059799
P30 MH075673
R25GM109441 (Hopkins PREP)
Tau Consortium (T-PEP-18-579974C)
Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease Venture Discovery Funding
Intramural Research Program
National Institute on Aging

Title: Inhibition of nSMase2 reduces tau transmission in Alzheimer's Disease mouse models

Authors: *M. HUANG;
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Abstract: Alzheimer's Disease (AD) remains the most prevalent form of dementia worldwide, with only minimally effective treatments. AD is clinically characterized by progressive cognitive decline and pathologically by the accumulation of two harmful proteins, Aβ and pTau. Recent studies have emphasized the role of extracellular vesicle (EV)s in the transmission of pathological tau between cells and have identified the partial inhibition of EV production using small-molecule inhibitors targeting nSMase2 as a potential therapeutic approach. However, no compounds suitable for clinical development have been discovered so far. Using high-throughput screening and extensive medicinal chemistry efforts, we identified PDDC as a highly selective and potent inhibitor of nSMase2. PDDC has excellent brain penetration and is orally bioavailable. To assess the impact of PDDC on tau propagation in vivo, we chronically administered PDDC-containing chow to PS19 transgenic mice. Following 5 months of dosing, we evaluated brain ceramide levels, nSMase2 activity, tau levels, glial activation, thickness of the hippocampal neuronal cell layer, and staining of synaptophysin in mossy fibers. Additionally, we isolated and characterized neuronally-derived extracellular vesicles (NDEVs) from plasma. To directly observe the PDDC effect on tau propagation, we also developed a mouse model where a P301L/S320F double mutant human tau-encoding adeno-associated virus (AAV) was stereotaxically injected into the hippocampus, and subsequent transfer to the contralateral dentate gyrus (DG) was monitored. Expression of mutant Tau in neurons lead to elevated nSMase2 activity and increased levels of ceramides in vitro. In vivo, chronic PDDC treatment restored abnormal levels of multiple ceramide species and nSMase2 enzymatic activity observed in the brains of PS19 mice. PDDC-treated PS19 mice showed reduced levels of total tau and Thr181-pTau in the hippocampus. PDDC treatment also reduced glial activation, increased mossy fiber synaptophysin immunostaining, and improved thickness of the pyramidal and granule cell layers. Additionally, the concentration of plasma NDEVs was reduced, and their p181-Tau levels were lower in PDDC-treated compared to untreated PS19 mice. A decrease in NDEVs carrying p181-Tau was further confirmed through flow cytometry analysis. In mice treated with PDDC after AAV-hTau seeding, there was a reduction in tau staining intensity in the contralateral dentate gyrus (DG). The data obtained from two AD models using PDDC strongly support the potential use of nSMase2 inhibition as a therapeutic strategy to slow down the spread of tau pathology in AD.

Disclosures: **M. Huang:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.17/F1

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

Support: FAPERJ E26/010.002284/2019
CNPq 313353/2021-2
FINEP 01.19.0103.00
CAPES 001

Title: Varenicline: a possible preventive treatment for cognitive deficits in an animal model of Alzheimer's disease.

Authors: ***V. DUARTE**[1], L. BALTHAZAR[2], A. BANDEIRA-MARTINS[2], A. CYPRIANO[2], R. DOUETS[2], A. NUNES-FREITAS[2], Y. ABREU-VILLAÇA[2], A. MANHAES[3];
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Abstract: Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, corresponding to 60% of cases of dementia, and was considered the 6th leading cause of death among the elderly in the USA. Objectives: The aim of this work was to test varenicline (VAR) as a preventive treatment for memory and learning deficits in a model of intracerebroventricular (ICV) infusion of β-amyloid peptide (Aβ) in Swiss mice. These parameters were observed through: 1) the changes in learning and memory behavior related to AD; and 2) the effects of the VAR treatment on the adopted model. Methods: 120 Swiss mice were used, the VAR treatment started at PN76 and continued until PN127. During this period, the animals were treated daily by gavage with: a) filtered water; b) VAR at a dose of 2 mg/kg/day. At PN90, the animals underwent surgery for the implantation of the osmotic minipump for ICV injection of the Aβ or the surgical control group. Control animals had their minipumps filled with vehicle (HEPES 4 mM + 0.22 nmol E-64 - cysteine protease inhibitor), while animals in group Aβ received infusion of the peptide (0.46 nmol Aβ + 0.22 nmol E -64). The tests were performed as follows: PN118 and 119 Passive Avoidance (PA) test; PN120 the Open Field (OF) test, and in PN121 the Object Recognition (OR). Results: In the OF test, no significant differences were observed for total exploratory activity [$F(5.43) = 0.95$; $p > 0.10$] and for variables associated with anxiety-like behavior [% Time at the Center: $F(5.43) = 0.68$; $p > 0.10$. % Entries at the Center: $F(5.43) = 1.09$; $p > 0.10$]. PA results suggest that VAR treatment partially reversed the memory impairments both after 3 h [$F(2.39) = 2.53$; $p = 0.09$] as after 24 h [$F(2.39) = 2.82$; $p = 0.07$]. In the OR, while control and VAR-treated Aβ animals showed marked increase in the interaction time with the newer objects, untreated Aβ animals showed no differences in behavior toward these objects in the 1.5 h and 24 h trials. Conclusion: Our data suggest that the use of VAR, in our experimental model, acts as a possible preventive treatment for cognitive deficits caused by the accumulation of Aβ peptide.

Disclosures: **V. Duarte:** None. **L. Balthazar:** None. **A. Bandeira-Martins:** None. **A. Cypriano:** None. **R. Douets:** None. **A. Nunes-Freitas:** None. **Y. Abreu-Villaça:** None. **A. Manhaes:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.18/F2

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

Support: NIH 5T32NS041218

Title: Novel tyrosine kinase inhibitors reduce pathology in mouse models of Alzheimer's Disease

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Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease of aging marked by extensive neuron death and subsequent cognitive decline. Primary pathological hallmarks of AD include amyloid-beta plaques composed of improperly cleaved amyloid precursor protein (APP), extensive neuroinflammation, and vascular fibrosis, which are believed to interact and result in subsequent neurodegeneration. However, putative therapeutic options for alleviating these features remain limited, emphasizing the need to develop comprehensive treatments for patients with AD. Our lab has previously demonstrated enzymes known as tyrosine kinases to be upregulated in postmortem AD brains and implicated in the regulation of autophagy, neuroinflammation, and vascular fibrosis, identifying them as potential targets for therapeutic intervention for treating AD. Utilizing recently synthesized novel small molecule tyrosine kinase inhibitors, I have demonstrated that tyrosine kinase inhibition reduces levels of neurotoxic protein aggregates, mitigates microglial-mediated neuroinflammation, and reduces vascular fibrosis, leading to improved behavioral outcomes in animal models of AD.

Disclosures: M. Stevenson: None. **X. Liu:** None. **M. Hebron:** None. **C.E. Moussa:** None.

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.19/F3

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

Support: NIA of the NIH GRANT AG077991

Title: Preclinical evaluation of a small molecule that inhibits tau self-association in transgenic mouse exhibiting mutant tau and APP

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Abstract: Accumulation of neuritic plaques and neurofibrillary tangles composed primarily of aggregated amyloid beta (Aβ) and tau proteins, respectively, are well established hallmarks of Alzheimer's disease (AD). A substantial amount of scientific evidence highlights a possible existence of crosstalk between Aβ and tau having synergistic effects. Evidently, aberrant Aβ expression leads to inflammation which affects tau phosphorylation and aggregation. While,

Amyloid aggregates develop after tau aggregates, suggesting a feedback mechanism that fundamentally drives AD progression. Hence, it is of interest to investigate if inhibition of tau self-association in the context of amyloid pathology blocks the initiation and progression of tau aggregation. This approach translated in vivo in htau and JNPL3 mouse models of tauopathy, wherein our orally available small molecule (OLX-07010) inhibited the accumulation of self-associated tau, insoluble tau aggregates, and total tau, and rescued impaired motor function (Davidowitz EJ et al., 2020 doi: 10.3233/JAD-190465; Patel DR et al., 2021 doi: 10.1002/alz.058326). The primary goal of the current study is to determine the preventive and therapeutic efficacy of OLX-07010 in reducing tau pathology in transgenic mice expressing tau and APP (TAPP). Short-term (3 months) and long-term (9 months) treatment studies of 3-month-old female TAPP mice will be performed with dosing in diet. In both treatment studies, there are 6 groups, wild type age-matched control mice (n=15), a 3-month-old baseline group (n=15), vehicle (n=20), and treatment groups receiving 20, 40 and 80 mg/kg (n=20, each). The primary endpoints of this study are the reduction of insoluble tau aggregates and Aβ. Acute treatment will evaluate the effect on tau aggregation that begins to appear at 3 months, and the chronic study will determine the same on the accumulation of Aβ plaques that begins at 8 months. Secondary endpoints will include amelioration of cognitive and motor behavior deficits, reduction of self-associated tau, self-associated Aβ and tau-Aβ interaction, and improvement in fluid biomarker assays for tau, amyloid, inflammation and neurodegeneration Additionally, immunohistochemistry of brain sections will be performed for tau, Aβ and markers of microgliosis and astrogliosis. The 9-month treatment study has started, and the 3-month study is timed to conclude in parallel with the 9-month study. This study is targeted towards studying the efficacy of our lead small molecule in reducing tau aggregation in the context of concurrent Aβ expression and inflammation for better evaluation of the pharmacology of OLX-07010 for clinical studies in AD.

Disclosures: D. Patel: A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Lopez:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **E. Davidowitz:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **J.G. Moe:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc..

Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.20/F4

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

Title: Standardized Extract of Ginkgo biloba modulates amyloid-beta in aged female mice with basal forebrain cholinergic dysfunction

Authors: *B. G. MURATORI[1], C. CAETANO[2], I. E. T. VEIGA[2], A. G. SOLIANI[2], R. P. URESHINO[2], S. M. CERUTTI[3];
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Abstract: Normal aging is related to anatomical and physiological alterations in the central nervous system, which have been associated with cognitive impairment in individuals aged 65 and over. Understanding brain changes during normal aging is necessary to further comprehend functional loss associated with neurodegenerative conditions, such as Alzheimer's disease. Late-onset Alzheimer's Disease (LOAD) is a progressive neurodegenerative disease marked by cognitive loss and behavioral changes, with a higher prevalence in elderly women. Extracellular deposition of misfolded amyloid peptides (Aβ) and intracellular formation of neurofibrillary tangles of hyperphosphorylated tau protein are known as the hallmarks of the disease. Decreased release of the neurotransmitter ACh is observed early in patients with LOAD, and the loss of basal forebrain cholinergic neurons is associated with memory impairment. Mouse models with reduced expression (knockdown - KD) of the vesicular acetylcholine transporter (VAChT) have been used as a model for studying LOAD. These mice have VAChT levels reduced by 65% (KDHOM) or 45% (KDHET), mimicking moderate and severe stages of LOAD, respectively. Currently, several treatments are available for LOAD, such as Donepezil, which inhibits acetylcholinesterase action. However, since LOAD is a complex condition, current treatments do not have a wide range of effectiveness. In this sense, a multi-target therapeutic might be more effective in the treatment of LOAD. The standardized extract of Ginkgo biloba has been used as a cognitive enhancer that has been used in both healthy and pathology models. Previous studies from our group have shown that EGb increases the number of pyramidal neurons expressing VAChT in the dorsal hippocampal formation of 3-month-old VAChT KD females, associated with the improvement of both object recognition and aversive memory. Therefore, the aim of this study is to evaluate the effects of chronic treatment with EGb on Object Recognition Memory (ORM) and Object Location Memory (OLM) in 24-month-old female wild-type (WT) and VAChT KD mice. Monomers of Aβ1-42 expression were analyzed in the dorsal hippocampus subfields (CA1 and CA3) and the dentate gyrus by immunohistochemistry. Our results show that EGb treatment modulates both ORM and OLM in aged female WT mice and both genotypes of VAChT KD mice. Additionally, EGb differentially modulated the number of cells expressing Aβ . Our data corroborate previous findings that showed a cognitive enhancement effect of EGb. Furthermore, it suggests a role in cholinergic signaling in mice with cholinergic hypofunction in a genotype-dependent manner.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.21/F5

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

Support: Intramural grant from NICHD,NIH

Title: Hippocampal Delivery of Neurotrophic Factor-a1/Carboxypeptidase E Gene Prevents Memory Loss in Alzheimer's Disease Mice

Authors: L. XIAO[1], X. YANG[2], P. SHARMA[3], D. ABEBE[2], *H. GAINER[4], Y. LOH[2]; [1]Section On Cell. Neurobiology, NICHD, NIH, Bethesda, MD; [2]NICHD,NIH, Bethesda, MD; [3]Xosomix, San Diego, CA; [4]ninds, Bethesda, MD

Abstract: Alzheimer's Disease (AD) has been increasing dramatically and > 6 million Americans are living with AD in 2023. Studies using therapeutic approaches targeting tau aggregation and amyloid pathology have not been very successful. Clinical studies of gene therapy with growth factor genes have shown some promise in reversing cognitive deficits. Here we show that viral-(AAV) delivery of human wild type or a non-enzymatic form (E342Q) of a trophic factor gene, Neurotrophic factor NF-α1/Carboxypeptidase E (NF-α1/CPE) produced remarkable effects on preventing development of cognition deficits and pathological changes in pre-symptomatic 3xTg-AD mice. Bilateral hippocampal injection of AAV- NF-α1/CPE or -CPE-E342Q was carried out to overexpress NF-α1/CPE or CPE-E342Q in 2-month-old 3xTg-AD mice and they were assayed at 7-8 months. Our results showed that AAV- NF-α1/CPE or CPE-E342Q gene delivery prevented cognitive dysfunction in these mice, as evidenced by intact memory and learning activity in Morris Water Maze test. This result indicates that this effect of NF-α1/CPE was independent of its enzymatic activity. Furthermore, biochemical studies revealed that pathological changes such as amyloid precursor protein expression were reduced in the AAV-NF-α1/CPE or -CPE-342Q treated versus non-treated 3xTg mice. Quantitative proteomics using isobaric TMT tags showed that NF-α1/CPE overexpression resulted in changes in signaling pathways related to CNS and axon development. In addition, changes in molecular pathways involved in DNA conformation and nucleosome assembly were also observed. These results suggest that NF-α1/CPE gene therapy can be a potential novel clinical approach to prevent or treat early onset of AD in patients.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.22/F6

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

Support: R01AG059799
R01AG063831

Title: Microglial-targeted nSMase2 inhibitor fails to reduce tau propagation in PS19 mice

Authors: *K. D. J. HUIZAR[1], M. HUANG[1,2], C. TALLON[1,2], H. JOHNSON[1], A. G. THOMAS[1], S. PICCIOLINI[7], M. BEDONI[7], X. ZHU[1,3], A. PAL[1], W. LIYANAGE[4], R. M. KANNAN[4,3], R. RAIS[1,2,5], B. S. SLUSHER[1,2,6,5];
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Abstract: Mounting evidence suggests that the cognitive decline associated with Alzheimer's disease (AD) is correlated with hyperphosphorylated tau (pTau) propagating between neurons along networks connected by synapses. It has been hypothesized this transcellular transmission occurs, in part, by extracellular vesicles (EVs). Ceramide, produced by the enzyme nSMase2 via hydrolysis of sphingomyelin, is critical for EV biogenesis. Both genetic and pharmacological inhibition of nSMase2 inhibits EV biogenesis and pTau propagation. There are no suitable nSMase2 inhibitors for clinical development thus far. Through a high-throughput campaign, our lab identified DPTIP, a highly selective and nM potency nSMase2 inhibitor. DPTIP, however, exhibits poor oral pharmacokinetics (PK), modest brain penetration, and rapid clearance; all of which limit its clinical translation. To enhance its PK properties, we conjugated it to a hydroxyl-PAMAM dendrimer delivery system, creating dendrimer-DPTIP (D-DPTIP), which was shown to selectively target microglia. In prior studies, using a murine AAV-hTau brain injection propagation model where tau was propagated mainly via microglial EVs, we showed that administration of D-DPTIP significantly inhibited the spread of tau. To further test D-DPTIP's efficacy, we used a PS19 transgenic model of AD. After 6 weeks of chronic dosing, total tau and pTau levels were quantified and nSMase2 target engagement assays in both microglial and non-microglial cells were conducted. We evaluated cognitive deficits assessed by Y-Maze and Novel Object Recognition Test and hippocampal volume loss assessed by Magnetic Resonance Imaging. We also used immunofluorescent (IF) staining and fluorescence-activated cell sorting (FACS) to determine cell types in the brain responsible for D-DPTIP internalization. Lastly, we used surface plasmon resonance imaging (SPRi) to characterize the origin of brain EVs released into plasma in PS19 mice ± D-DPTIP treatment. We report that D-DPTIP failed to alter tau or pTau in the PS19 mice. It also failed to reverse cognitive deficits and had no effect on hippocampal volume loss. Target engagement, IF, and FACS studies showed that microglia were the main cell type to internalize D-DPTIP. Lastly, SPRi analysis showed a decrease in levels of activated microglia-derived plasma EVs following treatment.
We conclude that the D-DPTIP selectively targets and inhibits nSMase2 in microglia. As a result, in the AAV-hTau seeded model, where microglial EVs play a central role, D-DPTIP was capable of inhibiting tau propagation. However, in PS19 mice, where neuronal-mediated tau propagation is prominent, D-DPTIP was ineffective.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.23/F7

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

Title: Effects of Tetrahydrocannabinol on the Healthy Brain and Alzheimer's Disease Pathologies in Mice

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Abstract: *Introduction:* Due to limited therapeutic options in Alzheimer's disease, new therapeutic approaches, including drug repurposing, might pave the way for effective treatments. In recent years, there has been growing interest in the potential therapeutic role of cannabinoids in Alzheimer's disease due to their neuroprotective and anti-inflammatory properties.The aim of this study was to evaluate the therapeutic potential of tetrahydrocannabinol (THC) in a mouse model of Alzheimer's disease, as well as the effect of THC on the healthy brain. *Material and Methods:* Adult C57BI/6J wild-type mice as well as transgenic 5XFAD Alzheimer mice were treated daily with 20 mg/kg THC for 6 weeks starting at 5 months of age (n=12-15 per group). Small-animal positron emission tomography (PET) was used to evaluate effects of THC exposure in treated mice and untreated age-matched controls *in vivo* (n=6 per group; nanoScan PET/CT, Mediso, Hungary). ^{18}F-Flourodesoxyglucose was used to evaluate the effect of THC on cerebral glucose metabolism in wild-type and 5XFAD mice, and ^{18}F-Florbetaben was used to determine amyloid load in 5XFAD mice. Tracer uptake was quantified in several brain regions. The Morris Water Maze was used to evaluate memory function (n=12-15 per group). *Results and Discussion:* THC-treated 5XFAD mice showed a significantly increased glucose metabolism in the hippocampus compared to untreated age-matched controls. Furthermore, ^{18}F-Florbetaben-PET detected a significantly lower amyloid load in THC-treated 5XFAD mice in several cortical regions compared to untreated age-matched controls. Additionally, THC rescued spatial reference memory deficits in 5XFAD mice. In contrast, ^{18}F-Flourodesoxyglucose-PET revealed a significant cerebral hypometabolism in THC-treated wild-type mice in several brain regions, along with spatial navigation deficits. Overall, we were able to demonstrate the harmful effect of chronic THC exposure on the healthy brain, while demonstrating its beneficial properties on Alzheimer's pathologies. THC displays an interesting therapeutic option for Alzheimer's disease that should be further evaluated in future studies despite its unfavorable effects on the healthy brain.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

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Program #/Poster #: PSTR073.24/F8

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

Support: NIH Grant : AG053150

Title: Treatment with OLX-07010 inhibits the aggregation of human P301lL tau in aged JNPL3 mice with dose dependence

Authors: *E. J. DAVIDOWITZ[1], P. LOPEZ[2], D. ROMERO[2], H. JIMENEZ[3], L. ADRIEN[3], P. DAVIES[3], J. G. MOE[1];
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Abstract: The P301L mutation in tau causes it to aggregate in human tauopathies (Hutton M, 2000) and has been used in tau constructs for developing transgenic mouse models of tauopathy. Endogenous murine non-mutated tau is not prone to aggregate and has been shown to inhibit the aggregation of human mutant tau in transgenic mice (Ando K et al., 2010). However, endogenous mouse tau does co-aggregate with pro-aggregant human tau expressed in mice (Hochgräfe K et al., 2013,). Treatment of young htau (doi: 10.3233/JAD-190465) and JNPL3 mice prevented the accumulation of tau aggregates. In this therapeutic study, homozygous female P301L 4R0N tau mice were aged to seven months and treated for five months with either 40 or 80 mg/kg OLX-07010 administered in feed. The Baseline group (n=20) was sacrificed at 7 months and the Vehicle and Treatment groups (n=25 each) were sacrificed at 12 months. The study was performed at an independent lab using blinded lots of feed. Initial evaluation of tau aggregation in brain lysates was performed with ELISAs formatted with antibodies DA31 and DA9 that recognize both the human P301L tau construct and endogenous murine tau. Self-associated tau was measured by mono-Antibody ELISA (DA9 capture; DA9-HRP reporter/detection), whereas large Sarkosyl-insoluble tau aggregates were isolated by ultracentrifugation. The readout from these assays indicated that the 40 mg/kg dose was as effective as the 80 mg/kg dose. To specifically determine the effect of OLX-07010 on the aggregation prone human P301L tau construct in homozygous female JNPL3 mice immunoblots were performed with the HT7 antibody specific for human tau. Minimally denaturing conditions were used to evaluate the aggregation of tau by immunoblot. Analysis of the immunoblot signal for human tau included very high molecular weight tau that remained at the top of the gel, tau oligomers and tau monomer. The signal from these tau species was normalized to total tau signal, and the baseline, vehicle and treatment groups were compared. The overall effect of OLX-07010 was similar using both ELISA and immunoblot approaches in that treatment inhibited tau aggregation above baseline. However, analysis of human P301L by immunoblot showed greater dose dependence as the 80 mg/kg dose was consistently more effective than 40 mg/kg dose for inhibiting tau aggregation. Although the immunoblot approach yields semiquantitative data, it enabled the visualization of the spectrum of human tau monomer and

aggregated species via resolution on a gradient gel and demonstrated greater dose dependence for the inhibition of P301L tau aggregation by treatment with OLX-07010.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.25/G1

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

Support: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
Conselho Nacional de Desenvolvimento Científico e Tecnológico
National Institute of Translational Neuroscience
International Brain Research Organization
Alzheimer’s Association (AARF-21-848798)
National Institutes of Health (NIH-NINDS/R01NS049442)
Serrapilheira Institute (R-2012-37967)

Title: Correction of mTORC1-mediated protein synthesis rescues memory in mouse models of Alzheimer’s disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by synapse failure and cognitive decline. Brain mRNA translation is central to synaptic plasticity and cognition, and converging evidence indicates it is impaired in AD. In particular, the mammalian target of rapamycin complex 1 (mTORC1) pathway plays a key role in regulating protein synthesis. Not surprisingly, the mTORC1 signaling has received considerable attention in recent AD research. However, results from such studies remain controversial. In this work, we analyzed the mTORC1 signaling proteins in hippocampi from mice infused intracerebroventricular (i.c.v.) with amyloid-β oligomers (AβO), the major neurotoxins in AD. We found a decrease in the levels of mTORC1 proteins in mice, 7 days after AβO infusion. Further, we tested whether enhancing mRNA translation could rescue defective translation and memory in mouse models of AD. Results show that haploinsufficiency for the translational repressors' eukaryotic initiation factor 4E binding protein 2 (4E-BP2) or Fragile X mental retardation protein (FMRP) prevented the inhibition of brain protein synthesis and memory impairment induced by AβO. These findings establish that targeting mRNA translation initiation corrects translational and memory deficits in AD models, and suggest a potential target to combat cognitive decline in AD.

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Poster

PSTR073. Therapeutic Strategies: Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.26/G2

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

Support: BrightFocus Foundation A2022017F
Alzheimer's Association 2019-AARF-643631
NIH R01 AG076610-01

Title: Impact of the niacin receptor HCAR2 in amyloid pathology and microglia response at late-stage disease

Authors: *M. MOUTINHO, I. CORONEL, S. PUNTAMBEKAR, M. A. BENITO, P. B.-C. LIN, S. GEIS, A. OBLAK, G. E. LANDRETH;
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Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease and a leading cause of dementia worldwide. Mounting evidence suggests that the accumulation and aggregation of amyloid-β (Aβ) is a key initiating factor in a cascade of events that lead to

AD. The AD brain is typified by a robust microglial immune response triggered by Aβ accumulation. Although microglia have emerged as an important player in AD pathogenesis and progression, the role of these cells in disease is complex and still not fully understood. We have recently described that the niacin receptor HCAR2 is required for an efficient microglial neuroprotective response in the 5xFAD amyloid mouse model. This analysis was performed at a stage of active and widespread plaque deposition and neuropathology. However, whether HCAR2 plays a role at a later stage of disease remains unknown. **Methods:** We analyzed the phenotype of 8-month-old 5xFAD male and female mice lacking the HCAR2 receptor. To examine if activation of HCAR2 exerts beneficial effects at a later stage of amyloid pathology, we treated a cohort of 8-month-old 5xFAD mice with the FDA-approved formulation of nicotinic acid (Niaspan®) by daily oral *gavage* for 30 days. **Results:** Our preliminary results show that the lack of HCAR2 exacerbates amyloid burden both at early and late stage in males and females. We also observed increased N-APP accumulation within dystrophic neurites of 8-month-old animals lacking HCAR2 suggesting aggravated neuropathology. Furthermore, treatment of 8-month-old 5xFAD animals with Niaspan® leads to decreased amyloid pathology. **Conclusions:** These preliminary data demonstrate that HCAR2 impacts amyloid pathology at later stages of disease, highlighting an important role of this receptor in disease and its potential as a therapeutic target. Treatment of 8-month-old 5xFAD mice with a FDA-approved agonist of HCAR2 leads to an array of salutary effects, suggesting that even at stages of severe amyloid deposition, neuronal dysfunction and neuroinflammation, this therapeutic strategy may be have beneficial effects. These data further support the potential of repurposing of FDA-approved formulations of nicotinic acid, such as Niaspan®, for the treatment of AD.

Disclosures: **M. Moutinho:** None. **I. Coronel:** None. **S. Puntambekar:** None. **M.A. Benito:** None. **P.B. Lin:** None. **S. Geis:** None. **A. Oblak:** None. **G.E. Landreth:** None.

Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

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Program #/Poster #: PSTR074.01/G3

Topic: C.03. Parkinson’s Disease

Support: DFG (HI 2154/2-1, Sachmittel)

Title: The impact of subthalamic nucleus deep brain stimulation in the beta range on cortical beta oscillations in Parkinson's disease patients

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Abstract: Neuronal oscillations and motor symptoms are closely linked in Parkinson’s disease (PD). Recordings from PD patients typically show pathologically enhanced oscillations in the beta band (13-35 Hz) in the subthalamic nucleus (STN) and other parts of the basal ganglia.

These oscillations can be modulated by means of deep brain stimulation (DBS), but whether and how DBS modulates cortical oscillatory activity remains a matter of investigation. Here, we aimed to examine whether it is possible to modulate cortical beta oscillations with STN DBS in the beta range. We recorded resting-state magnetoencephalography (MEG) from 18 PD patients implanted with a DBS system in the medication ON state. Bipolar DBS was administered through the left electrode at various frequencies in the beta range (10, 16, 20, 26, and 30 Hz) in a cyclic fashion, such that the stimulation turned on (5s) and off (3s) repeatedly. The pulse amplitude was set to 3 mA. Cyclic stimulation lasted 8 min for each frequency. We observed an increase of beta power during and shortly after stimulation (200ms post-stimulus). The peak frequency of this modulation had no obvious relation to the stimulation frequency and was clearest when DBS was applied at frequencies ≥ 20 Hz. The effect was strongest in sensors above sensorimotor regions in the stimulated (left) hemisphere. The topography of DBS artifacts, in contrast, was governed by the path of the cables connecting electrodes and pulse generator (right hemisphere). Our results suggest that we can modulate cortical beta oscillations by means of STN DBS in the beta range. Thus, it seems that DBS might be suited to probe the causal role of cortical beta oscillations for behavior.

Disclosures: L.M. Werner: None. **A. Schnitzler:** None. **J. Hirschmann:** None.

Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.02/G4

Topic: C.03. Parkinson’s Disease

Support: Ministry of Health & Welfare, Republic of Korea (grant number: HU21C0053)

Title: Functional brain networks of minor hallucinations and well-structured major hallucinations in Parkinson’s disease

Authors: *K. BAIK[1], Y. KIM[2], M. PARK[3], H. NA[1], S. CHUNG[1], H.-W. SHIN[4], Y. SOHN[1], Y. JEONG[2], P. LEE[1];
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Abstract: Background: Minor hallucinations (mHs) and well-structured major hallucinations (MHs) are common symptoms of Parkinson’s disease (PD) psychosis. The differences in resting-state networks (RSNs) between patients with PD without hallucinations (PD-nH), with mH (PD-mH), and with MH (PD-MH) are unknown. **Methods:** Total 73 patients were enrolled (27 PD-nH, 23 PD-mH, and 23 PD-MH). Using seed-based functional connectivity analyses, we

investigated the RSNs supposedly related to hallucinations in PD: the default mode network (DMN), executive control network (ECN), dorsal attention network (DAN), ventral attention network (VAN), and visual network (VN). We compared the cognitive function and RSN connectivity between the three groups. In addition, we performed a seed-to-seed analysis to examine the inter-network connectivity within each group using the corresponding RSN seeds.**Results:** PD-MH group showed lower test scores for attention, and visuospatial functions compared to those in the other groups. The connectivity of the right intracalcarine cortex within the DAN was lower in the PD-MH group than in the others. The PD-mH and PD-MH groups showed higher connectivity in the left orbitofrontal cortex within the DMN compared to the PD-nH group, whereas the connectivity was lower in the right middle frontal gyrus (MFG) within the ECN, precuneus cortex within the VAN, right middle temporal gyrus and precuneus cortex within the DAN, and left MFG within the VN. The PD-mH and PD-MH groups showed different inter-network connectivity patterns, especially regarding the DAN.**Conclusion:** DAN dysfunction may be a key factor in the progression from mH to MH in patients with PD.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.03/G5

Topic: C.03. Parkinson’s Disease

Support: Korean National Institute of Health Research Project 2021-ER1001-02

Title: Transcriptome analysis to identify pathological markers associated with sporadic Parkinson's disease

Authors: *S. YOO[1], J. CHANG[2], K. LEE[1], S.-I. KIM[1], Y.-M. SHIM[1], J. KIM[2], J.-K. WON[1], S.-H. PARK[1];
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Abstract: Parkinson's disease (PD) is a common neurodegenerative disease characterized by abnormal protein accumulation and the death of specific neurons, resulting in motor dysfunction. Research shows that neurodegenerative diseases share common pathological markers such as inflammatory response, reactive gliosis, and oxidative stress. Identifying genes regulating these cellular responses particularly in PD can help with diagnosis, understanding the disease environment, predicting progression, and evaluating therapeutic efficacy. In this study, we conducted single-nuclei RNA sequencing on the substantia nigra of four brains with sporadic PD and four brains diagnosed with primary age-related tauopathy (PART) to serve as a more appropriate control group from a pathological standpoint. We examined around 32,000 nuclei,

and identified marker genes for seven major cell types through cluster analysis. Differential expression gene analysis revealed more pronounced changes in non-neuronal cells like astrocytes and microglia compared to neurons themselves. These changes were associated with reactive glial features and inflammatory responses. Within the neuronal subset, we observed a decrease in dopaminergic neurons and an increase in GABAergic neuronal proportion. RNA velocity analysis showed notable differences in results between control and PD. The number of genes that were differentially expressed between control and PD was significantly higher in astrocytes and microglia. To gain further insight into disease-related cellular transitions in glial cells, we performed Monocle-based pseudotime analysis followed by TENET. Consequently, we discovered multiple genes that exhibited cell-type-specific expression and underwent disease-associated expression changes, enhancing their potential as pathological markers. These genes have undergone histological validation in postmortem tissues using single molecule in situ hybridization. Detailed new findings will be presented at the upcoming discussion.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.04/G7

Topic: C.03. Parkinson’s Disease

Support: RF1 MH121373
R01 NS097782

Title: Machine Learning-Based Differential Analysis of Brain White Matter Patterns in Parkinson's Disease and Essential Tremor

Authors: K. CHITTA[1], A. ALIJANPOUROTAGHSARA[2], A. SHALABY[1], J. CHOI[2], N. POURATIAN[2], ***J. LEE**[1];
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Abstract: Differentiating between Parkinson’s disease (PD) and essential tremor (ET) can pose a challenge in some cases as tremor can be a presenting symptom for both. Facilitating accurate diagnoses can ensure optimal initial treatment. Identifying relative differences between white matter (WM) microstructural changes between PD and ET can aid in differentiating these conditions as well as reveal underlying neurobiological mechanisms. In this study we used the multivariate machine learning (ML) model, XGBoost, to differentiate PD and ET subjects utilizing both average fractional anisotropy (FA) values and standard deviation of FA values, which quantifies the amount of dispersion of FA values from each region of interest (ROI). The study included 36 PD and 32 ET subjects that had deep brain stimulation (DBS) surgery due to moderate to severe motor symptoms. Pre-treatment diffusion tensor imaging (DTI) with 64

directions was performed for all subjects. All DTI images were preprocessed by performing skull stripping (BET) and eddy current correction before the computation of FA maps from diffusion tensors using DTIFIT. To extract quantitative measures from the FA maps, ROIs from the JHU white matter ICBM atlas were warped onto the native space of FA maps using the ANTS SyN registration method. The XGBoost model was optimized through hyperparameter tuning using HyperOpt and its performance was validated using a 5-fold cross validation (3:1:1 data split for training, validation, and test) approach to ensure the ML model's robustness. Additionally, relative contributions of important features were assessed using SHAP (Shapely Additive exPlanations) analysis. Our model achieved an AUROC of 0.784 and a balanced accuracy of 71.54% in distinguishing PD subjects from ET subjects, using imaging parameters alone. Among the important features, PD subjects exhibited significantly higher FA values relative to ET subjects in certain regions including the genu of corpus callosum (GCC), cingulate gyrus subregion of cingulum (CG), stria terminalis (ST) and superior longitudinal fasciculus (SLF). These findings suggest that FA values in specific ROIs have the potential to serve as valuable assets in characterizing and differentiating PD and ET. In summary, our study effectively investigated WM patterns in subjects with PD and ET using a multivariate ML technique, suggesting the presence of distinct WM microstructural differences in several brain regions, highlighting their potential as discriminatory biomarkers.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.05/Web Only

Topic: C.03. Parkinson's Disease

Support: MEX-PD is supported by the American Parkinson's Disease Association through a Diversity in Parkinson's Disease Research Grant (APDA/D07)
MER fellowship support from the Rebecca L Cooper Medical Research Foundation (F20231230)
ALF Grant scholarship (1222481) from CONACYT

Title: Mild cognitive impairment in Parkinson disease and its association with disease-related disability in Mexico

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Abstract: Mild cognitive impairment (MCI) affects a substantial proportion of individuals with Parkinson's disease (PD), with potential progression to dementia. Understanding the prevalence of MCI among people with PD in Mexico, an underrepresented population in research, is crucial for effective disease management. The aim of this study was to investigate the prevalence of MCI among Mexican PD patients and to test its association with PD-related disability levels. We used a subset of data from the Mexican Parkinson's Research Network (MEX-PD) consisting of a cohort of 200 PD patients (mean age ± SD; 68.3 ± 8.4) and 86 healthy controls (60.6 ± 7.8) from diverse regions across 16 states. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), with MCI defined as a score below 24. Disability levels were evaluated using the Hoehn-Yahr scale (HYs), ranging from 1 (mild) to 5 (severe disability). Our findings revealed a strikingly high MCI prevalence of 72.5% among Mexican PD patients, exceeding rates observed in other populations, such as Spanish and British cohorts, by 20%. In contrast, healthy controls exhibited an MCI prevalence of 32.5%. Years of education were significantly different between PD patients (mean years 12.18 ± 6.01) and healthy controls (14.88 ± 5.80). The level of disability significantly predicted inversely cognitive function scores in PD patients (ß=-1.99, $t(198)=-4.53$, $p<0.001$), with disability levels accounting for a significant portion of the variance in cognitive function scores ($R^2=0.09$, $F(6,193)=3.44$, $p=0.003$). Likewise, level of education significantly predicted directly cognitive function scores (ß=0.29, $t(198)=4.99$, $p<0.001$); this variable accounting for a significant portion of variance in cognitive scores ($R^2=0.11$, $F(1,198)=24.14$, $p<0.001$). Moreover, both disability levels and level of education significantly explain larger portion of variance in cognitive scores ($R^2=0.145$, $F(11,188)=4.07$, $p<0.0001$). Our results highlight the crucial role of disease severity and level of education in predicting cognitive decline in PD patients, highlighting the vulnerability of the Mexican population to MCI development compared to other cohorts. These findings raise intriguing questions regarding genetic, clinical, and environmental factors that may significantly influence cognitive function in the Mexican population. Exploring these factors could provide valuable insights into the underlying mechanisms of cognitive impairment in PD and pave the way for tailored interventions and improved patient outcomes in this population.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.06/G8

Topic: C.03. Parkinson's Disease

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Penn State College of Medicine Translational Brain Research Center
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Title: Susceptibility magnetic resonance imaging correlates with glial cell density in the parkinsonism red nucleus

Authors: *M. L. JOHNSON[1,3], M. M. LEWIS[2,3], E. W. WANG[2,3], L. C. JELLEN[2,3], G. DU[2,3], S. DE JESUS[2], L. KONG[2], C. PU[2], X. HUANG[2,3];
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Abstract: Background: Histological and magnetic resonance imaging (MRI) studies show the substantia nigra pars compacta (SNc) and red nucleus (RN) are similarly iron-rich. We previously showed robust correlations of susceptibility MRI metrics to glia and tau in the SNc, a key pathology site in parkinsonisms. Histopathological underpinnings of RN imaging in parkinsonisms is unclear. **Methods:** We evaluated 17 parkinsonism subjects and three controls with both *in vivo* MRI and postmortem pathology data. RN apparent transverse relaxation rate (R2*) and quantitative susceptibility mapping (QSM) values reflecting iron were derived from multi-gradient echo images. Archival midbrain slides stained with hematoxylin and eosin (H&E), or anti-α-synuclein, and anti-PHF-tau were digitized, color- and intensity-normalized, and quantified semi-automatically for RN neuron and glial cell densities, and percent area occupied by α-synuclein and tau staining. α-Synuclein and tau data were non-normal and thus log-transformed. MRI and histology associations were examined using Pearson correlation analyses[L1] . **Results:** All patients had similar mean (± standard deviation) RN neuron densities (16 cells/mm^2 ± 1.5) to those of controls, regardless of pathological diagnosis. Those with synucleinopathy had similar RN glial cell densities (690 cells/mm^2 ± 110) to controls. Progressive supranuclear palsy patients (n=4), however, had almost double that number (1258 cells/mm^2 ± 421). Subjects with pathological diagnoses had similar mean percentages of area occupied by α-synuclein (-4.49% ± 0.22), whereas controls had less (-4.96% ± 0.35). Progressive supranuclear palsy patients had a greater percentage of area occupied by tau (-3.50% ± 0.79) compared to those with synucleinopathy and controls (-4.60% ± 0.37). Among all subjects, RN

R2* and QSM did not correlate with neuron density, or percent area occupied by α-synuclein and tau (ps>0.209). RN R2* (r=0.52, p=0.0176) and QSM (r=0.56, p=0.0108), however, each associated with glial cell density. **Conclusion:** This is the first study to show that *in vivo* brain susceptibility MRI captured glial cell density in the RN of postmortem brains. Future studies are warranted to validate this finding for its potential scientific and translational values in understanding pathophysiological processes related to parkinsonian disorders.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Program #/Poster #: PSTR074.07/G9

Topic: C.03. Parkinson’s Disease

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Title: Black and African American Connections to Parkinson's Disease Study

Authors: *P. A. WILD CREA[1], M. B. MAKARIOUS[1], K. LEVINE[2,4], D. VITALE[3,4], M. KORETSKY[5], M. NALLS[3,4], Z.-H. FANG[6], D. A. HALL[7], T. XIE[8], M. PADMANABAN[8], E. A. SHAMIM[9], D. G. STANDAERT[10], M. DEAN[10], E. A. DISBROW[11], A. RAWLS[12], J. SOLLE[13], N. LOUIE[13], K. BILLINGSLEY[1], P. ALVAREZ JEREZ[3], D. HERNANDEZ[1], S. AREPALLI[1], L. MALIK[3], A. A. MIANO-BURKHARDT[1], H. LEONARD[3,4], H. A. IWAKI[3,4], C. A. BLAUWENDRAAT[1], A. A. SINGLETON[3], S. BANDRES CIGA[3], B. BLAAC PD STUDY GROUP[14], G. GLOBAL PARKINSON’S GENETICS PROGRAM[15];
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NY; [14]the Black and African American Connections to Parkinson's Dis. (BLAAC PD) Study, Bethesda, MD; [15]Global Parkinson's Genet. Program, Bethesda, MD

Abstract: Title: Black and African American Connections to Parkinson's Disease Study
Aim: BLAAC PD is a multi-center study recruiting Black and African American individuals with Parkinson's Disease (PD) and healthy controls. BLAAC PD aims to provide a platform for replication studies to explore the relevance of genetic findings reported in other populations and investigate genotype-phenotype correlations. The ultimate goal is to create a foundational cohort to assess diverse aspects of PD in this historically excluded population and serve as a model for diversity and equity in research.
Background: Understanding genetic mechanisms across diverse populations can provide unique insights into complex traits like PD. Our current insights of the genetics underlying PD etiology has been disproportionately based on European ancestry populations. This has led to a significant gap in our knowledge about the disease's genetics and clinical characteristics in underrepresented populations, particularly individuals of African and African admixed ancestries.
Materials & Methods: BLAAC PD collects samples from six sites across the United States. A total of 147 cases and 174 controls have been collected. Following DNA extraction, samples are genotyped and imputed, followed by ancestry assessment through a pre-trained machine learning model based on reference sample series. A comprehensive assessment was conducted to investigate known and novel genetic contributors. We also assessed structural variants in early-onset and familial PD cases.
Results: Our analyses showed consistent differences in variant frequencies, magnitude of effects, and risk alleles in genetic risk loci known to be associated with PD. Differences in variant frequencies, magnitude of effects, and risk alleles were also observed in known disease-causing mutations including SNCA, VPS35, LRRK2, PRKN, PINK1, DJ1 and GBA.
Discussion: These findings highlight the need for diverse representation in genetic research. Insufficiently diverse genetic data may exacerbate health disparities once translated to the clinic. BLAAC PD will help resolve the cross-ancestry applicability of drug targets, treatments and preventative measures by elucidating the genetic architecture of disease in African and African admixed ancestries and also providing a platform for replication studies of previous work in other populations. Looking ahead, BLAAC PD plans to continue recruiting and genotyping participants to serve as a foundational cohort for diverse genetic studies.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.08/G10

Topic: C.03. Parkinson's Disease

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Ministry of Science and Technology, Taiwan: MOST-110-2311-B-002-001-
National Taiwan University: NTU-112L104306

Title: Implications of piRNA candidates associated with Parkinson's disease

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Abstract: Parkinson's disease (PD) is a multifaceted disorder that arises from a complex interplay of genetic and environmental factors. Although several biomarkers, including different degree of α-syn aggregates and the neurofilament light chain, have been identified, the development of reliable and sensitive circulating biomarkers for PD remains a critical unmet need. Recent evidence suggests that piRNAs may be an emerging category of biomarkers, due to their (1) stability in biological fluids; (2) potential in packing into extracellular vesicles for transferring to long distance target tissue; (3) potential in mediated transcriptional control, both for the original cells generating these piRNAs and possibly performing transcriptional modulation when delivered to target cells via extracellular vesicle. With the disease-specific expression patterns and potential as modulators for disease pathogenesis, piRNAs can be considered as valuable markers for neurodegenerative diseases, and provide opportunities to understand disease mechanisms. We identified plasma piRNA candidates from small RNA sequencing datasets of our newly collected PD patient cohorts. The piRNA candidates were predominantly derived from a diverse range of transcripts, which we defined as piRNA units. By comparing our candidate biomarkers from plasma samples with a post-mortem brain small RNA sequencing dataset, we identified several units of piRNA candidates that may have potential for distinguishing PD patients with or without dementia from healthy control (HC). We have further revealed that putative regulatory regions of genes related to the respiratory electronic transport chain, facilitating molecules transport across the membrane, and chromatin remodeling, are differentially targeted by piRNAs in postmortem brain of PD with dementia patients compared to healthy controls, implicating possible pathological and therapeutic significance.

Disclosures: **P. Kung:** None. **Y. Tsai:** None. **M.J. Kuo:** None. **T. Ochiya:** None. **R. Wu:** None. **S. Lin:** None.

Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Program #/Poster #: PSTR074.09/H1

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01NS117547

Title: Exploring Local Gyrification Index Changes in Patients with Parkinson's Disease Experiencing Freezing of Gait

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Abstract: Introduction: Freezing of gait (FoG) occurs in around 50% of patients with Parkinson's Disease (PD). However, no objective methods exist to identify FoG in clinics. Morphological studies using T1-weighted (T1) MRI can inform about area, volume, and thickness changes but have been widely inconclusive. Local gyrification index (LGI) can inform about cortical folding and can be estimated from the T1-MRI using FreeSurfer. Though LGI has been proposed for almost a decade, it has only found recent attention in understanding PD-FoG. In this study, we attempted to replicate the previous finding with LGI deficits in PD-FoG using a well-characterized cohort of PD-FoG. We hypothesized that patients with PD-FoG will have a decreased LGI when compared to healthy controls and patients with PD who do not experience FoG (PD-nFOG). Methods: We recruited 53 participants at our site, of which 16 participants were classified as PD-FoG, 21 participants were classified as PD-nFoG, and 16 participants were healthy controls (HC). Diagnosis of PD-FoG was determined by direct observation of FoG by a movement disorders specialist during a physical therapy task designed to elicit FoG. All participants utilized in this study were scanned with the following T1-weighted MRI acquisition parameters on a 3T Siemens Skyra MRI scanner: resolution=1mm^3, TR/TE=2300/2.96ms. We processed the data using FreeSurfer 7.0 and computed LGI using the approach described by FreeSurfer. A manual and automatic quality check of the reconstruction was performed to verify the quality of data and reconstruction of cortical surfaces. We extracted mean LGI values from each region identified in the Desikan-Killiany atlas from each participant. Statistical comparisons were conducted using the PALM toolbox in FSL after regressing age, sex, handedness, levodopa equivalent daily dose, unified Parkinson's Disease Rating Scale, and intracranial volume. The results were considered significant at familywise error corrected (FWE) $p_{corr}<0.05$. Results: Our analysis showed there was no significant difference at FWE pcorr<0.05. Regardless of the FoG status, healthy controls showed a trend-level ($p_{corr}<0.1$) decreased LGI in several regions across the frontal, temporal, parietal, and occipital cortices. However, PD-FoG showed a trend-level ($p_{corr}<0.1$) higher LGI across the same regions when compared to PD-nFOG. Conclusion: Our

analysis suggested an increased LGI in PD-FoG while HC showed decreased LGI when compared to PD, regardless of the FoG status. Correlation between LGI and clinical/FoG symptoms is currently underway.

Disclosures: A. Gardner: None. **S. Lopez:** None. **Z. Mari:** None. **V. Mishra:** None.

Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Topic: C.03. Parkinson's Disease

Support: Nebraska DHHS LB692
Creighton Haddix Faculty Research Fund
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Title: Cns-derived exosomes in blood as biomarkers for parkinson's disease

Authors: *J. BAHN[1], H. KIM[2], M. S. BURNETT[3], J.-Y. HWANG[2];
[1]Med., [2]Pharmacol. and Neurosci., Creighton Univ., Omaha, NE; [3]Neurol., Creighton Univ. Sch. of Med., Omaha, NE

Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disease worldwide. PD is caused by severe loss of nigrostriatal dopaminergic neurons and is characterized by increases in cytoplasmic inclusions of α-synuclein. Identification of reliable biomarkers is critical for a timely diagnosis of PD. Although a recent study has reported αSyn-SAA technique with the high diagnostic accuracy of PD using cerebrospinal fluid, suitable laboratory tests are still quite limited and there are no blood-based tests available. In recent years, research on biofluid markers in PD has expanded, with particular emphasis on CNS-derived exosomes. Exosomes are nanovesicles that carry various proteins, lipids, mRNAs and microRNAs. Exosomes produced in the CNS can cross the blood-brain-barrier, making them a highly attractive source of biomarkers that can be isolated from peripheral blood. Several studies have shown a dysregulation of CNS-derived exosomes in PD patients' blood. These preliminary findings demonstrate the potential for clinical use of CNS-derived exosomal biomarkers in PD; however, research related to further validation and a large independent cohort study is needed for relevancy and accuracy. We conducted a pilot study to examine whether PD-related proteins, including α-synuclein, phosphorylated α-synuclein and DJ-1 in CNS-derived blood exosomes are significantly altered in PD patients *vs.* healthy controls. Toward this end, we isolated CNS-derived exosomes from blood samples of PD patients and controls and first, optimized the isolation protocol using healthy control blood samples. We confirmed successful isolation of CNS-derived exosomes with Western blot analysis on purified protein samples using antibodies against MAP2 and L1CAM. The results indicate that neuronal marker MAP2 is enriched in CNS-derived exosomes and neuronal exosome marker L1CAM is detected only in CNS-derived

exosomes. Next, to examine whether PD-related proteins are altered in CNS-derived blood exosomes, we performed Western blot analysis using the previously validated antibodies for α-synuclein, phosphorylated α-synuclein, PINK1, Parkin, and DJ-1. Our initial results demonstrate that DJ-1 levels are decreased in PD patients *vs.* controls. These are preliminary findings from a small group of samples within our total sample pool. As we expect to continue blood collection in these next few months, we will report our progress from further investigation. Ultimately, our study may provide additional insight into the effort to find novel biomarkers for diagnosis and monitoring of PD.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Program #/Poster #: PSTR074.11/H2

Topic: C.03. Parkinson's Disease

Support: NIH 5U01NS119562

Title: Impact of Harmonization on Automated Imaging Differentiation of Parkinsonism

Authors: *R. CHEN[1], W.-E. WANG[2], M. S. OKUN[3], A. BARMPOUTIS[4], D. E. VAILLANCOURT[2], A. STUDY TEAM[5];
[1]Biomed. Engin., [2]Applied Physiol. and Kinesiology, [3]Neurol., [4]Digital Worlds Inst., [5]Univ. of Florida, Gainesville, FL

Abstract: ComBat, a batch-effect correction tool developed for genomics, is employed to harmonize inter-scanner differences in diffusion tensor imaging. The aim of this study is to explore the impact of ComBat harmonized diffusion data on machine learning disease classification using a support vector machine. The two primary classification tasks in this study are: Parkinson's disease (PD) vs. atypical Parkinsonism (APD) (i.e., multiple systems atrophy - parkinsonian variant (MSAp) and progressive supranuclear palsy (PSP)) and MSAp vs. PSP. Using free-water (FW) and free-water corrected fractional anisotropy (FA_T) from 631 participants from sixty-three sites, we compared the machine learning performance of unharmonized diffusion metrics to ComBat harmonized diffusion metrics. Prior to training the model, we split the dataset at a ratio of 80:20, the resulting training and validation cohort had 524 participants and the testing cohort consisted of 107 participants. Then, two support vector machine models were trained, one using unharmonized diffusion data and the other using ComBat harmonized data. We used Delong's test to compare the two support vector machine models. Preliminary results indicate that ComBat harmonized diffusion data did not statistically improve the predictive performance of the machine learning model. Using the test cohort to compare the two machine learning models, we found that PD vs. APD was not statistically significantly different (P = 0.0916) and MSAp vs. PSP was found to not be statistically

significantly different (P = 0.130). This study suggests that support vector machines may not be susceptible to inter-site variability in diffusion imaging.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.12/H3

Topic: C.03. Parkinson's Disease

Title: Cognitive subtypes in Parkinson's Disease and Prodromal individuals: a cluster analysis approach

Authors: *E. GASPAR MARTÍNEZ[1], S. ALCAUTER[2];
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Abstract: Mild Cognitive Impairment (MCI) in Parkinson's Disease (PD) has proven valuable in identifying individuals at risk of developing dementia and has been described as a risk factor for individuals in the prodromal stage.A k-means clustering analysis was conducted to identify distinct cognitive profiles in 551 participants in the PD cohort (Age: 63 ± 9 years) and 361 in the Prodromal cohort (Age: 64 ± 6 years) from the Parkinson's Progression Markers Initiative Program (PPMI) (http://www.ppmi-info.org). The normalized scores of the 7 cognitive domains assessed in the Montreal Cognitive Assessment (MoCA) at the baseline visit were used as clustering variables (visuospatial/executive function, identification, attention, language, abstraction, episodic memory and orientation). Optimal cluster structure was determined using graphical and quantitative cluster validation methods.
Our clustering results revealed three distinct cognitive profiles for the PD patients: (1) Cognitively intact (n=260, 47.1%), (2) Mildly affected (n=239, 43.4%) characterized by an average performance of 0.45 in the episodic memory domain, and (3) Mostly affected (n=52, 9.5%) showed particularly lower average performances of 0.66, 0.35 and 0.36 in the language, abstraction and episodic memory domains, respectively. In the Prodromal cohort we identified three similar cognitive profiles: (1) Cognitively intact (n=171, 47.3%), (2) Mildly affected (n=124, 34.4%) exhibited an average performance of 0.41 in episodic memory, and (3) Mostly affected (n=66, 18.3%) characterized by average performances of 0.51 and 0.53 in language and episodic memory, respectively. Demographic characterization revealed significant differences in sex proportions among the subgroups in both cohorts, while only subgroups (1) and (3) in the Prodromal cohort showed significant age differences.
Our findings confirm the heterogeneity of cognitive deficits in PD, being the episodic memory domain the most affected in the subgroups with lower cognitive performance. Furthermore, we were able to identify cognitive profiles in the Prodromal cohort that are similar to those in

patients, indicating that similar cognitive deficits may be present in these subjects.Identifying MCI subtypes has proven valuable in identifying individuals at risk of developing dementia in PD, therefore identifying these cognitive profiles in the Prodromal population may be valuable to detect potential cognitive impairment at an earlier stage. Future studies should research into the clinical trajectory and neuroimaging correlates in these cognitive subtypes.

Disclosures: E. Gaspar Martínez: None. **S. Alcauter:** None.

Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Topic: C.03. Parkinson’s Disease

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Title: Exploring the potential of brain tissue-derived extracellular vesicles for Parkinson's disease biomarker discovery

Authors: *T. ARAB[1], Y. HUANG[1], R. NAGARAJ[2], E. GIZZIE[2], J. REDDING-OCHOA[1], J. C. TRONCOSO[1], O. PLETNIKOVA[3], T. BORONINA[1], J. W. SMITH[1], R. N. COLE[1], V. MAHAIRAKI[4], D. A. ROUTENBERG[2], K. W. WITWER[1];
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Abstract: Introduction: Parkinson's disease (PD) is a progressive movement disorder characterized by neurodegeneration. At present, the diagnosis of PD primarily depends on observing late-stage clinical symptoms, which can resemble those of other conditions. Extracellular Vesicles (EVs) play a crucial role in intercellular communication within the brain and may also migrate to peripheral biofluids like blood plasma, making them potential biomarkers of conditions including PD. In this project, we separated brain-derived EVs (bdEVs) from brain tissues and profiled their protein content. **Method:** Brain tissues were obtained from the Johns Hopkins Brain Research Center, including individuals with Parkinson's disease (n=24), progressive supranuclear palsy (PSP, n=25), and control subjects (n=24). bdEVs were separated as described previously (Huang, et al., JEV, 2020). bdEV characterization was performed per the MISEV2018 guidelines (Thery and Witwer, et al., JEV, 2018). Multiplexed ELISA identified bdEV surface proteins. A subset of the samples was profiled by 1) quantitative mass spectrometry and 2) data-independent mass spectrometry. **Results:** Microglial markers TMEM119 and CX3CR1, as well as neuronally enriched CD90, NCAM, and NRCAM, exhibited

significantly greater abundance (p-value < 0.05) in both PD and PSP compared with the control group. Quantitative proteomics identified 26 proteins were differentially abundant in PD compared with controls and/or PSP (log 2 fold-change > 0.32 and p-value < 0.05, n=5 each). Data-independent validation (n=10 each) confirmed that bdEV ANK1 and SLC4A1 could distinguish PD from both PSP and controls. **Conclusion:** We identified and validated several proteins with differing abundance in bdEVs obtained from brain of PD and PSP patients and controls. Additional research is now warranted to assess their potential biomarkers and therapeutic targets.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Program #/Poster #: PSTR074.14/H5

Topic: C.03. Parkinson’s Disease

Support: FAPESP
CAPES

Title: A non-expensive bidimensional assessment can detect subtle alterations in postural control in people in the early stages of Parkinson's disease

Authors: G. SANTOS[1], M. D'ALENCAR[1], A. FRAZÃO[2], A. ROQUE[3], J. MIRANDA[2], ***M. E. P. PIEMONTE**[4];
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Abstract: Background: Postural instability is a debilitating cardinal symptom of Parkinson's disease (PD). Its onset marks a pivotal milestone in PD when balance impairment results in disability in many activities of daily living. Early detection of postural instability by non-expensive tools that can widely be used in clinical practice is a key factor in preventing falls and all their negative consequences. **Objective:** To investigate the effectiveness of a two-dimensional balance assessment to identify the decline in postural control associated with PD progression. **Methods:** 55 people with PD, classified between early and moderate stages (stages I-III according to Hoehn and Yahr rated scale - H&Y), performed three clinical balance tests (Timed Up and Go, Balance Evaluation Systems Test, and Push and Release test) in addition to static stance test recorded by a two-dimensional movement analysis software. Based on kinematic variables generated by the software, a Postural Instability Index (PII) was created, allowing a comparison between its results and those obtained by clinical tests. **Results:** There

were differences between sociodemographic variables directly related to the evolution of Parkinson's disease. Although all tests were correlated with H&Y stages, only the PII was able to differentiate the first three stages of disease evolution (H&Y I and II: $p = .03$; H&Y 1 and 3: $p = .00001$; H&Y 2 and 3: $p = .02$). The other clinical tests were able to differentiate only the people with moderate PD stage (H&Y III). **Conclusion:** Based on the index provided by a two-dimensional movement analysis software that uses kinematic balance variables, it was possible to differentiate the postural control decline among the three first stages of Parkinson's disease evolution. This study offers a promising possibility of early identification of subtle changes in the postural control of people with PD in clinical practice.

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Poster

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Topic: C.03. Parkinson’s Disease

Support: New investigator Oregon medical research foundation grant

Title: Reliability and consistency of beta synchrony measures in Parkinson’s Disease : Findings from a multi-visit EEG study

Authors: *A. KAREKAL, B. SIMS, A. PRINCE, M. CARNES, C. MUNEZ, N. SWANN; Univ. of Oregon, Eugene, OR

Abstract: Parkinson’s Disease(PD) is characterized by abnormal beta (13-30Hz) oscillatory activity in thalamocortical network. Beta oscillatory activity is manifested in cortex with phase amplitude coupling (PAC) between beta phase and gamma amplitude (50-150Hz) and beta bursts. These measures are modulated in the sensorimotor cortex of individuals with PD compared to healthy controls and in response to therapy (Swann et al., 2015; Vinding et al., 2020). However, it remains unclear if these measures are reliable and stable over time. Therefore, we sought to understand if these measures are consistent over a month in healthy controls and patients both on and off medications. Additionally, we investigated whether the protocol for testing therapeutic response to medication (levodopa) yielded differences in beta synchrony measures (specifically, testing participants off and then on medication on the same day versus on 2 different days).
We analyzed beta synchrony measures in a cohort of 25 healthy controls and 24 individuals with PD using a 64 channel scalp electroencephalogram (EEG). Resting EEG recordings were performed in two different sessions, spaced approximately month apart. In the first session individuals with PD arrived off medication and resting EEG was acquired. Participants then took their medication and EEG was recorded again (all in the same day). In the second session, resting

EEG was recorded in individuals with PD on two different days, with randomized order for on/off medication testing. In both cases, off medication entailed at least 12 hours of medication abstention. For healthy controls, EEG was measured in the same way. PAC, burst duration and burst rate were computed for electrodes over the sensorimotor cortex (C3 and C4) and averaged. Our findings demonstrate a significant correlation in PAC and burst rate between sessions for healthy controls and individuals with PD in off medication state ($p<0.05$). In contrast, burst duration was correlated between sessions in healthy controls ($p<0.05$). Our study reveals that PAC and burst rate are relatively stable measured across a duration of a month. Future studies should explore the long-term changes in these measures with increasing disease severity in PD.

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Poster

PSTR074. Parkinson's Disease—Human studies: Genetics and Diagnostic

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Topic: C.03. Parkinson’s Disease

Support: NS119849
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Title: Performance fatigability in essential tremor and parkinsons disease

Authors: B. YACOUBI, S. DELMAS, J. KIM, J. HUBBARD, Y. CHOI, M. OKUN, ***E. CHRISTOU**;
Univ. of Florida, Gainesville, FL

Abstract: While fatigue, the subjective sense of tiredness, can be a common symptom in movement disorders (MDs), it may not necessarily reflect the actual decline in motor performance. Performance fatigability objectively addresses the decline in motor performance with sustained tasks and can provide valuable insights into the underlying mechanisms of MDs. Despite its profound impact, fatigability in MDs has received limited research attention. Here, we address this gap in knowledge by investigating fatigability in Essential Tremor (ET) and Parkinson Disease (PD) and examining its relationship with tremor (involuntary shaking of body parts). We performed three different studies. In the first study, we compared time to fatigue onset (tFO; defined as the inflection point indicating an increase in muscle activity or limb tremor) for 7 ET patients undergoing thalamic deep brain stimulation (tDBS) therapy. They sustained 30 s postural contractions with the deltoid muscles (shoulder flexion), quadriceps muscles (knee extension), and abdominal muscles (trunk flexion) with DBS ON and DBS OFF. In the second study, we tested 7 different ET patients undergoing tDBS. We compared time to task failure (tTF; length of time to sustain the task) during a seated postural arm task performed with DBS ON and DBS OFF. In the third study, we compared tFO for 23 PD patients and 27 healthy

controls (HC) during 120 s sustained force contractions with abduction of the index finger at 15% maximum. In all studies, we quantified tremor as the power from 4-8 Hz in the acceleration of the relevant body part. Study 1: Compared with the DBS OFF, DBS ON significantly prolonged tFO for the task performed with the deltoid muscles (71.8±20.4 %), quadriceps muscles (29.4±9.1 %), and abdominals (53.9±9.8 %). The DBS-induced suppression of upper limb tremor strongly associated with tFO prolongation of the deltoid muscles (R^2>0.79, p<0.05). Study 2: Compared with the DBS OFF, DBS ON significantly prolonged tTF for the seated postural arm task (37.1±9.1 %). The DBS-induced suppression of upper limb tremor significantly associated with the prolongation in tTF (R2>0.36, p<0.05). Study 3: Compared with HC, PD exhibited shorter tFO for the sustained force task (54.3±27.4 vs. 77.3±21.9 %). For all 40 participants, greater tremor associated with shorter tFO (R2=0.2, p<0.05). Our study provides novel evidence supporting the hypothesis that tremor significantly contributes to the amplification of fatigability in ET and PD. The implications are striking; interventions designed to mitigate tremor could, in turn, considerably diminish fatigability, as evidenced from our DBS findings.

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Poster

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Title: Progression of forearm rigidity in Parkinson's disease with and without REM sleep without atonia

Authors: *S. L. AMUNDSEN HUFFMASTER[1], M. E. LINN-EVANS[1], J. CHUNG[1], A. VIDENOVIC[2], M. J. HOWELL[1], P. J. TUITE[1], C. D. MACKINNON[1];
[1]Neurol., Univ. of Minnesota, Minneapolis, MN; [2]Neurol., Massachusetts Gen. Hosp., Boston, ME

Abstract: INTRODUCTION: We have previously shown that the expression and progression of gait deficits in Parkinson's disease is influenced by the presence of rapid eye movement (REM) sleep without atonia (RSWA), possibly due to degeneration of brainstem areas that control muscle tone during both wakefulness and REM sleep. We hypothesized that arm rigidity would progress more rapidly in PD with RSWA (PD+RSWA) compared to people with PD without RSWA (PD-RSWA) and healthy older adults.
METHODS: Thirty-two people with PD (15 PD+RSWA, 17 PD-RSWA, mean time since diagnosis = 2.2 ± 1.8 years) and 16 controls (age- and sex-matched) completed overnight polysomnography testing and quantitative rigidity testing at baseline and 35 ± 7 months. Rigidity testing was performed on both right and left forearms, with and without an activation maneuver (tapping the opposite hand on the leg). Rigidity was assessed using a custom manipulandum that passively rotated the forearm about the pronation/supination axis in a sinusoidal motion of ± 40 deg at 1.5 Hz. The primary outcome measures were peak negative power, angular impulse, and negative work. Linear mixed effects models (Rstudio) investigated the effects of group, visit, side (more vs. less affected, MA vs. LA), condition (activation maneuver, AM), and their interactions on the log10 transformed data. Significance was set to $p < 0.05$.
RESULTS: All three outcome measures showed significant main effects of side and condition such that the MA arm and AM condition had larger rigidity, respectively. However, group x condition interactions highlighted that the AM increased rigidity in the PD groups only. Additionally, the PD+RSWA group had higher rigidity than controls in the AM condition. When models were run with only the PD groups, there was a significant main effect of visit, but no significant interactions of visit, reflecting that the groups did not significantly differ in progression over 3 years.
CONCLUSION: These findings demonstrate that the rigidity progressed comparably across PD groups over 3 years, which was contrary to our hypothesis. In contrast, we have previously shown that gait impairment is significantly accelerated in the PD+RSWA individuals, but less so in PD-RSWA. Thus, gait impairment and forearm rigidity have different dynamics of progression in PD with and without RSWA.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.01/H9

Topic: C.04. Movement Disorders other than Parkinson's Disease

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FCT - Foundation for Science and Tecnology, I.P., under the project 2022.02008.PTDC
Graduate Women in Science - Nell Mondy and Nessa Notchev Fellowship 2022-2023

Title: Movement initiation reveals a hyperactive direct pathway in a mouse model of DYT-TOR1A dystonia

Authors: *F. F. DE BARROS[1], M. D. MENDONÇA[1], D. B. PEREIRA[1], D. S. MELO[1], L. RAUSCHENBERGER[3], S. KNORR[3], C. IP[3], R. COSTA[4], A. J. OLIVEIRA-MAIA[2], J. ALVES DA SILVA[1];
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Abstract: Dystonia is a movement disorder characterized by involuntary muscle contractions that yield abnormal movements and postures, which can be triggered or worsened by movement initiation. The striatum, a major input structure of the basal ganglia, plays a central role in the control of voluntary movement. Inputs provided to striatal medium spiny neurons (MSNs) are integrated by two parallel pathways - the direct pathway (responsible for action selection, involving D1-MSNs) and the indirect pathway (responsible for inhibiting competing actions, involving D2-MSNs). Theoretical models propose that an imbalance of these two pathways drives the abnormal muscular activity pattern characteristic of dystonia. However, there is a lack of *in vivo* evidence focusing on the activity of D1- or D2- MSNs upon movement initiation in dystonia. To this end, in a mouse model of the most common form of inherited dystonia (DYT1-TOR1A), we explored the activity of genetically identified MSNs during self-paced movement. Adult female and male DYT-TOR1AΔGAG knock-in (DYT) mice and wild-type (WT) littermates expressing Cre recombinase under the control of the dopamine D1 or A2A receptors (for D2 populations) were used. These mice were submitted to a standardized right side sciatic nerve crush (SNC) - a procedure known to induce dystonic-like movements (DLMs). To ascertain this, we used the tail suspension test (TST) to evoke DLMs and quantified them automatically using high-resolution video and markerless pose estimation. A Sham group, where the sciatic nerve was exposed but not crushed, was also evaluated. We found that DYT mice (n=11), but not WT (n=13) or Sham (n=8) mice, showed a significant increase in the number of DLMs of the injured hindlimb 9 weeks after the SNC. Furthermore, we used in vivo calcium imaging coupled with high-resolution video and head-mounted accelerometers to monitor D1- and D2-MSNs activity while mice explored an open field (OF), before and up to 9 weeks after the SNC. In the OF test, DYT, WT and Sham mice had no significant differences in the overall time spent locomoting, the speed ranges attained, and the time spent in each speed at any stage of the evaluation. However, the activity of D1-MSNs positively modulated by movement initiation significantly increased in DYT mice (n=6) when compared to WT (n=9) and Sham (n=4) mice, 9 weeks after the SNC. Conversely, the activity of D2-MSNs of WT mice (n=5) showed an increasing trend when compared to DYT (n=6) and Sham (n=5) mice at the same timepoint. Our results shed light on the pathophysiology of DYT-TOR1A dystonia by revealing a hyperactivity of D1-MSNs at movement onset.

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Poster

PSTR075. Dystonia and Related Disorders

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.02/H10

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CCXDP Grant

Title: Heterozygous KO female mice express Taf1 at normal levels in brain but show phenotypic effects

Authors: *E. M. CROMBIE[1], A. KORECKI[4], B. A. ADAIR[4], K. CLEVERLEY[1], T. J. CUNNINGHAM[2], W. LEE[5], T. C. LENGYELL[6], C. MADURO[1], V. MO[4], L. M. SLADE[4], I. ZOUHAIR[1], E. M. FISHER[3], E. M. SIMPSON[7];
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Abstract: TATA-box binding protein-associated factor 1 (TAF1) dysfunction is implicated in neurodevelopmental defects and neurodegeneration. Missense mutations in *TAF1* (Xq13.1) cause X-linked intellectual disability. X-linked Dystonia-Parkinsonism (XDP), a progressive neurodegenerative condition, is caused by a retrotransposon insertion into intron 32 of *TAF1*, linked to downregulation of a brain-specific *TAF1* isoform (Makino et al. 2007). Human XDP brains show striatal atrophy and late-onset motor impairment similar to that in Huntington Disease, which has also shown reduced TAF1 expression (Hernandez et al. 2020). Since TAF1 is a key component of the TFIID transcription initiation complex, how *TAF1* dysregulation predominantly affects the brain is not clear. Here, we generated the first mutant mouse model of *Taf1* loss of function. This C57BL/6J-*Taf1*^{em2Ems} mouse carries a conditional Cre-lox allele, with loxP sites flanking exon 8. Ubiquitous deletion of *Taf1* at an early embryonic stage resulted in generation of female heterozygous but not hemizygous males. When heterozygous females were bred with WT males, no *Taf1* KO females or males were recovered. These findings suggest that hemizygous *Taf1* deletion is embryonically lethal in male mice. Female carrier mice were analysed to determine the effects of heterozygous *Taf1* deletion. RT-qPCR showed no significant differences in expression of protein-coding transcripts between WT (n=6) and heterozygous KO (n=6) females. Western blotting of TAF1 expression showed no quantifiable difference between genotypes. Immunofluorescent staining of striatum showed that female carrier mice had strong TAF1 expression in all cell nuclei. Thus, *Taf1* mRNA and protein expression were unchanged in

heterozygous deletion mice, indicating compensation for the deleted *Taf1* allele. Assessment of weight and behaviour in heterozygous KO females (n=16) compared to control mice (n=16) showed surprisingly that mutant females weighed more (p=0.0265), travelled significantly less in the Open Field Test (p=0.0003), and crossed less into the centre zone (p=0.0463). Behaviour results were not correlated with weight. Increasing the total number of mice (n=32/genotype) showed that weight significantly increased with age (p=0.0001). Taken together, X-inactivation may be skewed in females resulting in *Taf1* expression from the WT allele. However, weight and behaviour phenotypes indicate that carrying the deleted *Taf1* allele may produce subtle *in vivo* effects. In future, we are genetically engineering mice to express human TAF1 containing the SVA to understand how TAF1 dysfunction causes XDP.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.03/I1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: European Joint Programme on Rare Disease (EJP RD-1352019)
European Union's Horizon 2020 research and innovation program under EJP RD COFUND-EJP No.825575 (EurDyscover)

Title: Gene-environment interaction elicits dystonia-like features that are associated with impaired translational regulation in a DYT-TOR1A mouse model

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Abstract: DYT-TOR1A is the most common inherited form of dystonia, a movement disorder characterized by involuntary movements and repetitive co-contraction of agonistic and antagonistic muscles. DYT-TOR1A is due to a glutamic acid deletion in the *TOR1A* gene and has a disease penetrance of only 30%. Despite knowing the etiopathogenesis, DYT-TOR1A pathophysiology remains unclear. The low penetrance indicates a gene-environment interaction, trigged by a genetic and/or environmental factor. Previous studies have shown that a peripheral nerve crush, acting as the environmental trigger, induces a dystonia-like phenotype in genetically predisposed rodents. In this study, we used high-throughput technologies to investigate the relation between the DYT-TOR1A mutation and the environment by performing a sciatic nerve crush on a DYT-TOR1A KI mouse model, carrying the human TOR1A mutation.
Dystonia like movements (DLM) were assessed by a deep learning network during the tail

suspension test (TST). RNA- and miRNA-sequencing on the ipsilateral cerebellar, contralateral striatal and cortical tissue were carried out to study the pathophysiological pathways of the DYT-TOR1A dystonia.
Following the sciatic nerve crush injury (crush), both DYT-TOR1A KI and wildtype (wt) mice exhibited DLM in the ipsilateral paw. Over the course of the 12-week experiment, however, wt crush animals were able to recover and return to lower DLM. This is in contrast to their DYT-TOR1A KI counterpart who sustained more DLM until the course of the 12 weeks. Using RNA-sequencing (RNAseq), we found more differentially expressed genes (DEGs) in the cerebellar tissue of the wt crush mice than in DYT-TOR1A KI crush mice. Pathway analysis of the DEGs in wt crush mice revealed translation-associated process, that were absent in the enrichment analysis of the DYT-TOR1A KI crush DEGs. In comparison, the number of cortical and striatal DEGs were higher in DYT-TOR1A KI than in the wt crush mice. Here, DYT-TOR1A KI DEGs were enriched in pathways linked to translational, but also to the biogenesis of ribonucleoprotein complexes. In support of the RNAseq data, altered levels of several miRNAs connected to translation regulation were likewise found in the same brain areas.
The DYT-TOR1A KI crush mice showed a more severe clinical phenotype, compared to the DYT-TOR1A KI naive mice, and the wt crush mice. The analysis of RNA and miRNA hint towards the regulation of translational processes in the cerebellum being a resilience mechanism in wt crush mice. The lack of such mechanism combined with the cortical, and striatal translational dysregulation might be the underlying cause for the dystonic phenotype in DYT-TOR1A KI crush mice.

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Poster

PSTR075. Dystonia and Related Disorders

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.04/I2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: DMFR-MCMD-2022-2
NIH Grant 7R01NS122990-02

Title: DYT6 dystonia protein THAP1 regulates spingolipid metabolism in the CNS.

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Abstract: Dystonia is a disabling neurological disorder that manifests as prolonged involuntary twisting movements. DYT-THAP1 is an inherited form of isolated dystonia caused by mutations in *THAP1*, which encodes the transcription factor THAP1. This factor has an established function in neurodevelopment and myelination. In prior studies, we identified that THAP1 has a cell-autonomous role in the generation of mature oligodendrocytes, the cell type responsible for the formation of the myelin sheath—a lipoprotein membrane composed of 70% lipids. We investigated whether THAP1 has a direct role in regulating lipid content that contributes to its role in myelination and CNS development. Through transcriptomic analyses, we identified that THAP1 regulates pathways relevant to the metabolism of sphingolipids, which are lipids enriched in the CNS and contribute to many processes, including regulating neuron-glia interactions. Subsequently, we performed comprehensive lipidomic studies using mass spectrometry on purified oligodendrocyte and neural progenitor cultures and brain tissue. These analyses revealed sphingolipid abnormalities in oligodendrocyte cultures and the CNS *in vivo* resulting from the loss of THAP1. Furthermore, we demonstrate from biochemical analyses that the loss of THAP1 results in the loss of activity of the sphingolipid catabolism enzyme Galactosylceramidase (GALC), resident in the lysosomes. Our studies identify the dystonia protein THAP1 as a CNS lysosomal lipid metabolism regulator.

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Poster

PSTR075. Dystonia and Related Disorders

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.05/I3

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIEHS Grant ES029344

Title: Pathophysiological changes across multiple brain regions in the Slc39a14-knockout mouse model of childhood-onset manganese-induced dystonia-parkinsonism.

Authors: *A. N. RODICHKIN, J. L. MCGLOTHAN, R. KAPOOR, T. R. GUILARTE; Envrn. Hlth. Sci., Florida Intl. Univ. Robert Stempel Col. of Publ. Hlth. & Social Work, Miami, FL

Abstract: Childhood-onset manganese (Mn)-induced dystonia-parkinsonism (COMnDP) is a rare and debilitating motor disorder. Over the last decade, numerous clinical reports describe loss-of-function mutations in the Mn-transporter gene *SLC39A14* resulting in COMnDP. In the context of severe dystonia (DY) and cerebellar (Cb) atrophy, *SLC39A14* mutation carriers present with up to 20-fold increase in blood Mn levels and high brain Mn deposition as evidenced by T-1 weighted MRI. The affected individuals develop motor deficits as early as 6-months of age and are refractory to L-DOPA which is the primary pharmacological approach in

idiopathic Parkinson's disease. Although parkinsonism is typically associated with the disease, DY is central to its clinical manifestation. Yet, the underlying pathophysiology and mechanisms of DY remain largely unexplored. We have previously characterized a novel *Slc39a14*-knock-out (KO) murine model of the human disease from the perspective of the dopaminergic (DAergic) system of the basal ganglia (Rodichkin et al. 2021, 2022). We reported that the *Slc39a14*-KO mice expressed locomotor, balance, and gait deficits and DY-like features. We also showed that DAergic neurons of the substantia nigra pars compacta do not degenerate. However, we discovered 70-90% inhibition of striatal DA release. Human cases of the disease and the murine model have a very complex behavioral phenotype that is unlikely to be explained by the inhibition of DA release alone. In the current studies, we show that in the presence of elevated Cb Mn levels (12-13-fold increase, $p<0.0001$, n=6) the *Slc39a14*-KO postnatal day 60 (PN60) mice manifest a decrease in normal physiological tremors (genotype effect in males (M) $p=0.004$, in females (F) $p<0.0001$) implicating Purkinje cell dysfunction. Furthermore, TSPO autoradiography, a well validated biomarker of neuroinflammation, revealed a marked increase in TSPO levels across numerous regions of the hindbrain, including the Cb, Cb cortex ($p=0.0157$, n=6 in M and $p=0.0140$, n=5-6 in F) and the brainstem (BrSt) ($p=0.0038$, n=6 in M and $p=0.0076$, n=5-6 in F). An increase in the levels of TSPO is suggestive of ongoing neuropathological changes. To further investigate neurodegenerative changes in the hindbrain of PN60 *Slc39a14*-KO mice, we performed immunohistochemistry for the microglial marker Iba-1 in sagittal brain slices, revealing marked and highly localized microglia activation and clustering within deep cortical regions of the Cb and select nuclei of the BrSt. To our knowledge this is the first report that delineates potential neurodegenerative changes in the Cb and BrSt of *Slc39a14*-KO mice as a preclinical animal model of COMnDP.

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Poster

PSTR075. Dystonia and Related Disorders

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.06/I4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: The Collaborative Center for X-Linked Dystonia-Parkinsonism

Title: Transcriptomic profiling of human postmortem brain tissue in X-Linked Dystonia-Parkinsonism

Authors: M. G. MURCAR[1], A. DOMINGO[1], R. YADAV[1], C. VAINE[1], S. REED[1], S. ERDIN[1], J. LEMANSKI[1], C. E. F. DE ESCH[1], C. FERNANDEZ-CERADO[2], S. VELASCO-ANDRADA[2], P. LAGARDA[2], E. MUNOZ[3], M. A. ANG[3], C. C. E. DIESTA[4], L. OZELIUS[1], E. B. PENNEY[1], M. TALKOWSKI[1,5], *C. BRAGG[5,1];
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Abstract: X-linked dystonia-parkinsonism (XDP) is an adult-onset neurodegenerative disorder that occurs almost exclusively in males from the Philippines. Affected individuals share a founder haplotype that includes an SVA insertion in *TAF1* intron 32, and functional analyses in cell lines reveal alternative splicing (AS) and retention of the intronic region (IR) proximal to this genetic defect. Further, CRISPR-excision of the SVA insertion represses these transcriptomic signatures and rescues canonical *TAF1* transcript downregulation in patient-derived neural stem cells. To determine whether these molecular footprints are mirrored in tissue, we established an XDP-specific brain bank to acquire postmortem brain samples and leverage the high prevalence of this globally rare disorder in an island in the Philippines. Our first-of-its-kind facility in the country set up infrastructure in a rural and medically underserved province. We established an institutional and community coalition to encourage brain donation, enabling the collection of 94 whole brains within an initial 7-year period: 63 from XDP-affected individuals and 31 from control individuals (20 males and 11 females). Disease course, age at onset and death, and genotype were consistent with known features of XDP, and mean postmortem interval was < 30 hours. We profiled tissue from 19 affected individuals and 8 controls, including from disease-relevant brain structures such as the striatum and cerebellum. Targeted RNA sequencing of *TAF1* revealed disease-specific AS in intron 32 in all 15 brain regions profiled, recapitulating observations in cell lines, as well as significant retention of this intron, especially in structures that have been associated with XDP in prior neuropathological studies. Transcript assembly and annotation revealed isoform- and brain region-specific reduction of *TAF1* expression that correlated with age at onset in specific brain structures. Thus, our strategy of discovery *in vitro* recovers molecular signatures in brain tissue, and leads to biologically relevant insights into tractable disease signatures. Furthermore, we showcase the opportunities of resource initiatives for unique genetic Mendelian disorders such as XDP.

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Poster

PSTR075. Dystonia and Related Disorders

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant R01DC015216
NIH Grant K24DC018603

Title: Preliminary network changes in action-specific focal dystonia using individualized cortical parcellation

Authors: *Y. WANG[1], D. HU[2], M. CHEN[3,4], B. HUYNH[1], J. A. BURNS[5], H. LIU[6,2], T. J. KIMBERLEY[1,2];
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Abstract: Action-specific focal dystonia (ASFD) manifests as abnormal muscle contraction in a body part during the performance of certain complex and highly trained actions like speaking or writing. While there is emerging evidence for altered cortico-subcortical network functioning underlying such action specificity, the pathophysiology of ASFD remains unclear. In this ongoing study, we investigate functional network differences between subjects with ASFD and healthy controls. Notably, we use individualized cortical parcellations which adjust network boundaries to minimize within-network heterogeneity, thus offering greater accuracy than population-level atlases alone and enabling comparisons in both network topography and connectivity cortically.
Preliminary resting-state fMRI dataset was collected from subjects with ASFD (*N*=22 with laryngeal dystonia, LD; *N*=8 with focal hand dystonia, FHD) and healthy controls (*N*=20, HC). After standard preprocessing in FreeSurfer, individual brains were parcellated into a) 18 networks and b) 92 networks in native space. Jaccard coefficients were computed to quantify between-subject network spatial similarities using the *fsaverage6* surface. Functional connectivity (FC) was computed as Pearson's *r* between mean network BOLD signals. *A priori* regions of interest (ROI) based on prior research included sensorimotor areas, operculum, inferior parietal lobule (IPL), basal ganglia, thalamus, and cerebellum.
18-network parcellations revealed atypical inclusion of middle superior temporal gyrus (mSTG) in sensorimotor network in subjects with ASFD, but not HCs. This ROI in operculum was consistent with network-35 in 92-network parcellations, which showed significantly higher spatial similarity in LDs than in HCs (*p*<0.001). FC analyses showed the inclusion of mSTG in the inferior sensorimotor network involving tongue/larynx was likely driven by significantly increased FC between network-10 (sensorimotor representation of larynx) and network-35 in LDs (*p*=0.017), accounting for sex, age, and symptom duration. Preliminary results also revealed significant FC differences between LDs and HCs involving other sensorimotor regions, operculum, and IPL.
Our preliminary results suggest the involvement of mSTG in the pathophysiology of ASFD during rest without symptom engagement, similar to task-related changes in mSTG that have been previously reported. Increased connectivity between mSTG and sensorimotor larynx network may reflect increased demand for auditory monitoring of speech in LD, while more data are needed to elucidate the potential disease mechanism for FHD.

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Poster

PSTR075. Dystonia and Related Disorders

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Topic: C.04. Movement Disorders other than Parkinson's Disease

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Title: Reversing pathology and associated motor impairments in a murine model of Vanishing White Matter Disease via eIF2B activation

Authors: K. A. LIN[1], *D. L. DONNELLY-ROBERTS[1], H. M. ROBB[1], K. WILLIAMS[1], R. N. SADOWSKI[1], M. M. SHEEHAN[1], V. A. KURSCHNER[1], M. E. KORT[1], A. SERONE[2], S. SANYAL[2], C. SIDRAUSKI[2], E. G. MOHLER[1];
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Abstract: Vanishing White Matter Disease (VWM) is a rare neurodegenerative disorder characterized by progressive deterioration of white matter in the central nervous system and consequent impaired motor function. No treatments currently exist for this fatal leukodystrophy. Partial loss-of-function mutations in an essential translation initiation factor, eukaryotic initiation factor 2B (eIF2B), cause the disease. Activation of eIF2B releases the global translational brake induced by the integrated stress response (ISR) and attenuates induction of transcriptional ISR targets. A compound that activates eIF2B has the potential to treat VWM, as well as other diseases characterized by prolonged and excessive induction of the ISR.In mice, pathology can be induced by a mutation in the eIF2B5 gene (e.g., R195H human/R191H mouse). R191H homozygous (HO) mutants provide a murine model that recapitulates many aspects of VWM disease, such as spontaneous myelin loss, progressive ataxia, and motor skill deficits. Chronic oral administration of eIF2B activators has previously demonstrated prevention or attenuation of motor symptoms in the VWM mutant mouse model, but treatment with an eIF2B activator was initiated in these experiments well before the onset of symptoms or at a specific age when only some of the mice were symptomatic.In the current study, we initiated treatment of individual mice only after they displayed impaired motor behavior, as measured by the balance beam assay. Drug-in-diet with a novel eIF2B activator was administered to the R191H HO mice upon the onset of these disease symptoms, which ranged in age from 25-28 weeks for females and 26-34 weeks for males. Treatment continued for 4 months from the start of dosing with behavioral measures and clinical observations captured longitudinally. At the end of the study, mice were euthanized humanely; brains, spinal cord and plasma were collected. Study endpoints included gene expression, pharmacokinetic measures, and histological markers. Behavioral assays showed significant reversal of motor impairments with dose-dependent improvement in the balance beam assay. Body weights also improved in a dose-dependent manner after initiation of compound administration. Gene expression and immunohistochemistry analyses are on-going; past studies in this VWM mutant mouse model have consistently demonstrated an induction of ISR-hallmark gene expression and increased protein ISR markers, which were attenuated by eIF2B activator

treatment. The current study extends previous findings by demonstrating that motor impairment deficits can be reversed even when treatment is delayed until mice are fully symptomatic.

Disclosures: **K.A. Lin:** A. Employment/Salary (full or part-time):; AbbVie Inc. **D.L. Donnelly-Roberts:** A. Employment/Salary (full or part-time):; AbbVie Inc. **H.M. Robb:** A. Employment/Salary (full or part-time):; AbbVie Inc. **K. Williams:** A. Employment/Salary (full or part-time):; AbbVie Inc. **R.N. Sadowski:** A. Employment/Salary (full or part-time):; AbbVie Inc. **M.M. Sheehan:** A. Employment/Salary (full or part-time):; AbbVie Inc. **V.A. Kurschner:** A. Employment/Salary (full or part-time):; AbbVie Inc. **M.E. Kort:** A. Employment/Salary (full or part-time):; AbbVie Inc. **A. Serone:** A. Employment/Salary (full or part-time):; Calico Life Sciences. **S. Sanyal:** A. Employment/Salary (full or part-time):; Calico Life Sciences. **C. Sidrauski:** A. Employment/Salary (full or part-time):; Calico Life Sciences. **E.G. Mohler:** A. Employment/Salary (full or part-time):; AbbVie Inc.

Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.09/I7

Topic:

Support: AMED under Grant Number JP19ek0109216

Title: The longitudinal change of serum neurofilament light chain levels with the progression of motor impairment symptom in polyglutamine disease model marmoset

Authors: ***T. NAKATANI**[1], A. KOSUGI[1], H. TATEBE[2], T. TOKUDA[2], L. M. BYRNE[3], E. J. WILD[3], Y. NAKAMURA[1], S. NOGUCHI[1], M. KOIZUMI[1], A. KAWANOBE[1], S. KOJIMA[1], N. NOGAMI[1], Y. SAGA[1], K. OWARI[1], Y. SAITO[4], E. N. MINAKAWA[1], K. SEKI[1];
[1]Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [2]Inst. for Quantum Med. Science, Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan; [3]UCL Queen Square Inst. of Neurology, Univ. Col. London, London, United Kingdom; [4]Dept. of Neuropathology, Tokyo Metropolitan Geriatric Hosp. and Inst. of Gerontology, Tokyo, Japan

Abstract: Neurofilament light chain (NfL) is a biomarker that indicates neuronal damage and can serve as a biomarker for disease onset and progression in neurological diseases. For spinocerebellar ataxia 3(SCA3), a polyglutamine disease, cross-sectional studies have shown higher NfL levels in the blood and cerebrospinal fluid of patients compared to healthy controls and also established a correlation between disease progression and NfL levels (Wilke et al., 2020). Therefore, NfL holds potential as a biomarker for detecting disease onset and reflecting disease progression in SCA3. However, a drawback of the cross-sectional studies is the significant variance in NfL levels among patients, limiting its use as a potential biomarker. The longitudinal studies, which track the disease progression of the same subjects over time, could overcome this issue. However, this approach has proved difficult in humans due to the long

monitoring periods required to observe the generally gradual progression of symptoms. To address this challenge, we utilized a marmoset model of polyglutamine disease (Tomioka et al.,2017). They are carrying human ataxin3 cDNA with abnormally elongated CAG repeats, which encodes the polyglutamine stretch responsible for spinocerebellar ataxia 3. This animal model offers several advantages for conducting longitudinal studies. They experience a shorter time to disease onset compared to humans, and their body size enables repeated sampling of serum without compromising their health. We assessed the motor function of 4 transgenic animals (TGs) by a ladder-climbing task (Kosugi et al., 2023, SfN abstract (see companion presentation)). During the two-year study period, 3 out of the 4 TGs exhibited a decline in ladder climbing speed. Within 12 months, 2 of them became completely unable to climb the ladder. The remaining one maintained consistent climbing ability. Throughout the study, we collected serum samples from the 4 TGs and 5 age-matched wild-type controls (WTs) every 2-3 months. Serum NfL levels were measured using ultra-sensitive single-molecule arrays (Simoa). When comparing climbing speed and NfL levels, we found that TGs experiencing a decrease in speed maintained higher serum NfL levels than WTs immediately before the speed decline. However, we found no correlation between NfL levels and the decrease in speed. The TG that did not exhibit a decline in speed maintained NfL levels similar to the WTs. These findings suggest that while serum NfL levels may not accurately reflect the progression of motor function impairment, they can still serve as a biomarker for disease onset, aligning with cross-sectional studies conducted in humans.

Disclosures: **T. Nakatani:** None. **A. Kosugi:** None. **H. Tatebe:** None. **T. Tokuda:** None. **L.M. Byrne:** None. **E.J. Wild:** None. **Y. Nakamura:** None. **S. Noguchi:** None. **M. Koizumi:** None. **A. Kawanobe:** None. **S. Kojima:** None. **N. Nogami:** None. **Y. Saga:** None. **K. Owari:** None. **Y. Saito:** None. **E.N. Minakawa:** None. **K. Seki:** None.

Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.10/I8

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: AMED 19ek0109216h0003

Title: Revealing progressive motor impairment in a transgenic marmoset model of polyglutamine disease through a high-throughput behavioral phenotyping system

Authors: *A. KOSUGI[1], M. KOIZUMI[1], A. KAWANOBE[1], N. NOGAMI[1], S. KOJIMA[1], Y. SAGA[1], Y. SAITO[2], T. NAKATANI[1], K. OWARI[1], K. SEKI[1];
[1]NCNP, Tokyo, Japan; [2]Tokyo Metro Ist Gerontol, Tokyo, Japan

Abstract: With the recent advancement of gene modification techniques, several non-human primate (NHP) models of neuromuscular diseases have been developed. One problem for NHP

genetic research is an inadequate sample size to detect common behavioral phenotypes, especially since the genetic background of NHP is heterogeneous, which can cause variability in their behavior. For instance, while we have previously generated a transgenic marmoset model of the polyglutamine (polyQ) disease (Tomioka et al., 2017), the number of behavioral tests has been limited because of the time-consuming nature of animal training and testing. Here, we have developed a high-throughput behavioral phenotyping system that utilizes passive monitoring of naturalistic behavior that does not require animals to train in advance and automated video analysis. Then, we aimed to characterize the progressive motor impairment in PolyQ disease marmosets by systematically applying this system from infancy to adulthood. For the experiment, we utilized a total of 11 healthy adult common marmosets and seven transgenic marmosets with polyQ disease. Our analysis focused on the marmosets' climbing behavior, which is a naturalistic behavior for them, considering their arboreal habitat. We developed in-house ladder apparatus composed of a transparent rectangular acrylic box where the rungs were vertically arranged on the front surface. Their behavior was continuously recorded by a high-speed camera placed in front of the apparatus for five minutes. Applying markerless tracking by deep learning, the positions of the limbs were tracked, and the climbing speed, stride length, and contact duration to the ladder rung were calculated. The results revealed a significant decrease in climbing speed among PolyQ disease marmosets compared to their healthy counterpart. Notably, four animals exhibited a consistent pattern of progressive decline in climbing speed. Furthermore, a detailed analysis demonstrated the distinct characteristics of each animal. Some displayed a decrease in stride length, while others demonstrated an increase in contact duration while maintaining the same stride length. Electrophysiological and pathological analysis revealed further insights. The former animals showed fasciculation-like involuntary electromyographic activity, and peripheral nerve degeneration, suggesting neurogenic muscle atrophy, whereas the latter animal showed a loss of Purkinje cells without muscle atrophy, suggesting cerebellar ataxia. Through our system, we were able to characterize a shared behavioral phenotype in polyQ disease marmosets and elucidate the underlying neurological mechanisms.

Disclosures: **A. Kosugi:** None. **M. Koizumi:** None. **A. Kawanobe:** None. **N. Nogami:** None. **S. Kojima:** None. **Y. Saga:** None. **Y. Saito:** None. **T. Nakatani:** None. **K. Owari:** None. **K. Seki:** None.

Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.11/J1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS Grant R00NS110878

Title: Conditional Knockout of Gnal in the Striatum Produces Dystonia-Like Motor Symptoms

Authors: *N. E. CHAMBERS[1], D. HALL[1], J. LANGMAN[1], M. KAPLAN[1], T. CURRY[4], S. GARAN[4], J. CLIKAS[4], M. MILLETT[2], M. S. MOEHLE[3];
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Abstract: GNAL-linked dystonia is an adult onset disorder associated with symptoms of abnormal muscle clenching and twisting of the limbs. GNAL is a gene which encodes the alpha subunit of the heterotrimeric G protein, Galpha olf. GNAL is expressed abundantly in the striatum, but it is not yet known what effects striatum-specific knockout will have on activity of spiny projection neurons and downstream brain nuclei in the direct and indirect pathway. To begin to address the role of striatal Gnal in the pathophysiology of dystonia, we injected Gnal floxed/floxed mice with adeno-associated viruses to express Cre recombinase or fluorophore control to remove expression of Gnal in the striatum of adult mice Using this viral mediated adult striatal conditional knockout model, we investigated the contribution of striatal Gnal to dystonia symptoms and circuit dysfunction using behavioral, electrophysiological, and biochemical, and calcium imaging techniques.. Our results reveal that striatal Gnal knockout causes hindlimb clasping and dystonia like movements during tail suspension, slowed fine motor movements in the Erasmus ladder, and slips during the ledge test, suggesting that these mice show a robust dystonia-like motor phenotype. Furthermore, we observed alterations in activity of striatal spiny projection neurons and on resulting GABA release on terminals in the SNr and GPe. Finally, we observed alterations in calcium activity that correspond to motor deficits in the Gnal striatal conditional knockout mouse. Taken together, these results suggest that this mouse model is an exciting tool with which to study Gnal-linked dystonia and that targeting cellular and circuit dysfunction in the striatum may help to alleviate dystonic motor symptoms.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.12/J2

Topic:

Support: NIH/NINDS R00NS110878

Title: Conditional Knockout of Gnal in Cerebellum Produces Dystonia-Like Motor Symptoms

Authors: *J. LANGMAN[1], N. CHAMBERS[1], D. HALL[1], T. CURRY[1], M. KAPLAN[1], L. SANCHEZ[1], J. CLIKAS[1], M. MILLETT[2], M. S. MOEHLE[3];
[2]Pharmacol., [3]Pharmacol. & Therapeut., [1]Univ. of Florida, Gainesville, FL

Abstract: GNAL-linked dystonia is an adult onset disorder which is characterized by abnormal muscle clenching and twisting of the limbs. GNAL is a gene which encodes the alpha subunit of

the heterotrimeric G protein, Galpha olf . Within the brain, GNAL is expressed abundantly in the cerebellum, but cerebellum-specific contributions to this form of dystonia are unknown. Therefore, in the current study we stereotaxically injected the cerebellum of Gnal floxed/floxed mice with adeno-associated viruses to express Cre recombinase or fluorophore control to remove expression of Gnal in adult mice. Using this viral mediated adult knockout model, we investigated how loss of Gnal in the cerebellum leads to dystonia symptoms and circuit dysfunction using electrophysiological and behavioral techniques. Cerebellar Gnal conditional knockout animals showed slowed fine motor movements in the Erasmus ladder and pole test, difficulty balancing on the ledge test, and dystonia like movements. To further narrow down the contribution of specific cerebellar neurons to these symptoms, we crossed an L7 cre mouse line to our Gnal floxed mice, thus producing embryonic conditional knockout of Gnal which is selective for Purkinje neurons. Overall, we found that these mice had behavioral deficits which were comparable to those of adult cerebellar knockout mice. This suggests that Purkinje neurons contribute to GNAL-linked dystonia symptoms. Finally, we found alterations in Purkinje neuron firing patterns via ex vivo electrophysiology. Overall, the results of this study show that the cerebellum may be involved in the pathology of GNAL-linked dystonia.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.13/J3

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH T32-NS082128-06
F31NS131000

Title: Deficits in executive functioning and processing speed contribute to exacerbated endpoint control in advanced Essential Tremor

Authors: *S. DELMAS[1], A. RATAJSKA[2], Y. CHOI[1], B. YACOUBI[1], M. S. OKUN[3], D. BOWERS[2,3], E. A. CHRISTOU[1,3];
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Abstract: Essential Tremor (ET) is the most common movement disorder in humans. The cardinal sign of ET is a bilateral 4 - 8 Hz upper limb action tremor. Although ET is often characterized in the context of tremor, >30% of individuals with ET exhibit cognitive deficits and have a 400% greater likelihood of developing mild cognitive impairment (MCI) and dementia relative to the general population. Moreover, ET patients with cognitive deficits exhibit exacerbated motor difficulties that are not explained by features of tremor (amplitude, location,

type). Despite this, findings connecting cognitive deficits with an underlying motor symptom in ET remain elusive. Here, we recruited 14 individuals with advanced ET and 14 age- and sex-matched healthy controls. Both groups performed a simple motor task that used goal-directed contractions with the ankle and only the individuals with ET participated in a battery of neurocognitive assessments. Raw scores from the individual cognitive measures were demographically (age, gender, and/or education) normed and converted to Z-scores. Composite scores were then calculated for the following cognitive domains: (1) recent memory, (2) executive function, (3) language, (4) visuospatial skill, and (5) processing speed. For the motor task, participants performed 50 unloaded, goal-directed pulse movements with a spatial/temporal target of 9 degrees in 180 ms. These contractions are accomplished by preplanned descending cortical commands and not affected by online feedback or tremor. We quantified performance as the endpoint error and trial-to-trial relative variability. Endpoint error, which represents the shortest distance from the target, was calculated as the hypotenuse of the target-normalized spatial and temporal errors. Endpoint variability, which represents the consistency of performance, was calculated as the trial-to-trial coefficient of variation (CV) of the hypotenuse of the target-normalized produced position and time. We found that endpoint error ($p < 0.05$) and variability ($p < 0.01$) were significantly higher in the ET group compared to the healthy control group. Interestingly, in the ET group, greater endpoint error is associated with worse executive function whereas greater endpoint variability is associated with worse processing speed. Associations across other cognitive domains were not significant. In summary, we provide novel findings addressing how cognitive deficits exacerbate motor control in ET.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.14/J4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH R01AI147496

Title: Selenoprotein I is required for ether lipid homeostasis and proper myelination in brain

Authors: *L. NUNES[1,2], C. MA[3], F. W. HOFFMANN[3], P. R. HOFFMANN[3], M. W. PITTS[3]; [1]Univ. of Hawaii John A. Burns Sch. of Med., Honolulu, HI; [2]Anatomy, Biochemistry, and Physiol., [3]Dept. of Cell and Mol. Biol., Univ. of Hawaii, Honolulu, HI

Abstract: Selenoprotein I (SELENOI) is an endoplasmic reticulum resident phosphotransferase that catalyzes the final reaction of the CDP-ethanolamine branch of the Kennedy pathway of phospholipid synthesis. In this pathway, SELENOI is required for the efficient synthesis of phosphatidylethanolamine (PE) and plasmenyl-PE, which are important phospholipids that

contribute to cellular membrane composition. Although present in various cell-types throughout the body, plasmenyl-PE is particularly enriched in white matter of the central nervous system (CNS). Plasmenyl-PE is characterized by a vinyl ether bond that is preferentially targeted by reactive oxygen species. In this manner, plasmenyl PE acts as an antioxidant that protects against peroxidation of polyunsaturated fatty acids in membrane phospholipids. *In vitro* studies have shown that SELENOI ablation disproportionally affects plasmenyl-PE levels, a finding corroborated in patient-derived fibroblasts with rare SELENOI loss-of-function mutations. Of further significance, SELENOI mutations lead a complex form of hereditary spastic paraplegia (HSP), a neurodegenerative condition affecting upper motor neurons characterized by impaired functionality of the lower limbs. Given the putative importance of SELENOI to the brain, we developed a mouse model of CNS-restricted SELENOI deficiency that circumvents the embryonic lethality caused by constitutive SELENOI knockout (KO) in mice. This was achieved using a transgenic strain previously used for CNS-specific KO studies, where Cre recombinase is driven by the tubulin-1α promoter (*Tuba1a-Cre)*. Resulting mice (*Tuba1a-Cre::SELENOI$^{fl/fl}$*) exhibited striking alterations in brain ether lipid composition, which coincided with severe motor deficits and brain pathology including impaired myelination, elevated reactive gliosis, and microcephaly. In summary, these findings detail the critical importance of SELENOI-derived plasmenyl-PE for neurodevelopment.

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Poster

PSTR075. Dystonia and Related Disorders

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.15/J5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Temozolomide Induces Contractions of GAA Repeats via DNA Base Excision Repair to Attenuate Frataxin Deficiency in Friedreich’s Ataxia

Authors: Y. LAI[1], R. ARMBRISTER[1], N. DIAZ[1], Y. CEYHAN[2], I. AGOULNIK[2], ***Y. LIU**[1]; [1]Chem. and Biochem., [2]Human and Mol. Genet., Florida Intl. Univ., Miami, FL

Abstract: Friedreich's Ataxia (FRDA), the most prevalent form of recessive ataxia, is caused by the expansion of GAA repeats in the first intron of the frataxin (*FXN*) gene. The repeat expansion leads to the silencing of the *FXN* gene expression; presently, there are no effective treatments for FRDA. Our previous study has shown that temozolomide (TMZ), an anti-brain tumor drug, can induce GAA repeat contractions in FRDA patient lymphoblasts through the DNA base excision repair (BER) pathway suggesting that TMZ-induced alkylated DNA bases on GAA repeats recruit BER enzymes, causing the expanded repeats to contract. We further hypothesize that TMZ can induce GAA repeat contraction to upregulate the *FXN* gene expression *in vivo* through BER. We found that TMZ treatment induced massive GAA repeat

contractions in FRDA transgenic mouse cerebellar neurons and FRDA neural cells differentiated from FRDA patient iPS cells, leading to an increased expression level of FXN protein in FRDA neurons and mouse brain tissue, as well as elevated BER capacity in the mouse brain, heart, and other tissues. We further elucidated the molecular mechanisms underlying TMZ-induced GAA repeat contraction in that TMZ led to opened chromatin by inhibiting H3K9 methyltransferase activity and the production of repressive histone mark H3K9me3 in FRDA neuronal cells. This further resulted in an even distribution of alkylated DNA bases in the expanded GAA repeats of the *FXN* gene and Pol β-mediated BER through which GAA repeats are contracted. Our study provides proof of concept that the crosstalk between endogenous BER and inhibition of H3K9 methylation in FRDA neural cells can result in GAA repeat contraction. Our results will open a new avenue to developing a novel gene therapy by targeting histone methylation and the BER pathway as an effective treatment for repeat expansion diseases.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.01/J7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01NS058784

Title: A comprehensive flow cytometry panel allows temporal profiling of immune responses in rat brain after ischemic stroke

Authors: *Y. ZATULOVSKAIA[1], M. C. S. BOSHUIZEN[1], F. DU[1], X. LIANG[1], S. A. MICHIE[2], T. M. BLISS[1], G. K. STEINBERG[1];
[1]Neurosurg., [2]Pathology, Stanford Univ., Stanford, CA

Abstract: Rat models are widely used in neurological studies, such as stroke research, as they are better suited than mice for behavior studies and various brain imaging techniques. However, methods for investigating immune responses and identifying different leukocyte subsets in rats, a key component of stroke research, lag behind the mouse due to lack of specific antibodies for flow cytometry and transgenic rat models. Several flow cytometry antibody panels have been used to study the immune response of the rat brain after stroke, but these panels did not distinguish between pro- and anti-inflammatory macrophages, which is essential for stroke-induced neuroinflammation research. Here, we developed flow cytometry panels to measure myeloid and lymphoid leukocyte subsets in rat brain, blood, and spleen, with a specific focus on macrophage subtypes, and validated them in an ischemic stroke model. Adult male (8-12 weeks old) Nude and Sprague Dawley (SD) rats were subjected to distal middle cerebral artery occlusion to induce cortical ischemic stroke. Ipsi- and contralateral hemispheres, blood, and

spleen were collected and analyzed by flow cytometry at different time points post-stroke. Cell populations were sorted using FACS, and then characterized using real-time qPCR or morphological analysis to confirm our flow cytometry gating strategy. We were able to discriminate microglia, 3 monocyte/macrophage subsets, granulocytes, dendritic cells, NK cells, B cells, and T cells in the brain and periphery. The temporal profile of different leukocyte subpopulations after stroke resembled those reported in mice, providing confidence in the reliability of our antibody panel: granulocytes and monocytes peaked in the first 2-3 days post stroke, B and T cells peaked around 4-5 days, followed by a gradual increase of proliferating resident 'microglia' over 14 days. Using a combination of CD43 and His48 to distinguish monocyte/macrophage sub-populations we observed a shift in monocyte/macrophage sub-populations over time after stroke, akin to the shift from pro- to anti-inflammatory macrophages reported in mice stroke-injured brains. Notably, Nude rats were different from the SD rats in regard to His48 expression, with SD rat brain monocyte/macrophage population being predominantly His48lo, whereas Nude rats had both His48lo and His48hi sub-populations. Overall, our development of flow cytometry panels for rats that distinguish various leukocyte subsets, including monocyte/macrophage sub-populations, provides a valuable tool to investigate the complex immune responses in rat models of neurological disorders.

Disclosures: **Y. Zatulovskaia:** None. **M.C.S. Boshuizen:** None. **F. Du:** None. **X. Liang:** None. **S.A. Michie:** None. **T.M. Bliss:** None. **G.K. Steinberg:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.02/J8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Central nervous system T-cell alterations in post-traumatic stress disorder

Authors: *S. M. CALDERAZZO[1], A. C. MCKEE[2], B. R. HUBER[3];
[1]Pathology, [2]Boston Univ., Boston, MA; [3]VA Boston Healthcare, Boston, MA

Abstract: Post-traumatic stress disorder (PTSD) is a clinically diagnosed psychiatric disorder characterized by intrusive and hypervigilant anxiety with increased risk for suicide and cognitive impairment but is currently poorly treated with available therapies. The pathophysiology in human PTSD brains is not well defined, but numerous imaging studies describe impaired frontal cortex activity. Notably, peripheral blood analyses of PTSD patients show increased inflammatory cytokines and effector T-cells that associate with symptom severity. Recent research identified central nervous system (CNS) associated T-cells in the meninges and perivascular spaces of healthy brain tissue. These CNS T-cells are largely resident memory phenotypes that monitor the tissue for pathogens and support essential neuron function via cytokine secretion. Despite reports of peripheral T-cell alterations, there are no studies investigating CNS T-cells in human PTSD. In this study we collected post-mortem brain tissue

from 18 clinically diagnosed PTSD individuals (average age: 57.17 years) and 18 age-matched controls (average age: 57.75 years) to assess CD8 and CD4 T-cell in the frontal cortex and overlying meninges via multiplex immunofluorescence. All subjects in this study are male due to the low number of female donors in our brain bank and exclusion criteria included individuals with other psychiatric disorders, neuropathological diagnoses, or severe inflammatory diseases. Our preliminary data shows a trend of increased CD8+ T-cells in the meninges (p=0.08) of PTSD individuals with a loss of CD4+ T-cells in the meninges (p=0.051) and gray matter (p=0.024). Additionally, we find fewer CD8+ T-cells express resident memory markers (Gray Matter: p=0.031; White Matter: p=0.048; Meninges: p=0.073) suggesting an increase of other T-cell subtypes. Each T-cell subtype expresses discrete cytokine and signaling molecules and a shift away from resident memory phenotypes may indicate a change in T-cell function during disease. Overall PTSD has distinct CNS T-cell alterations that may affect their signaling pathways and ultimately influence neuronal activity. We are currently investigating cytokine expression and association with other pathological measures to further determine the role of T-cells in PTSD and aid in identifying novel therapeutics.

Disclosures: S.M. Calderazzo: None. **A.C. McKee:** None. **B.R. Huber:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.03/J9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA R01AA025591

Title: Adolescent intermittent ethanol is not sufficient to drive neuroinflammation nor escalate drinking in male rats

Authors: *J. WOODEN[1], L. PEACOE[1], C. ANASOOYA SHAJI[1], C. CHANDLER[2], M. BARDO[2], K. NIXON[1];
[1]Univ. of Texas, Austin, Austin, TX; [2]Univ. of Kentucky, Lexington, KY

Abstract: During adolescence the brain is highly susceptible to alcohol-induced damage and a subsequent neuroimmune response, effects that may drive the development of an alcohol use disorder (AUD). Microglia and astrocyte reactions have been associated with adolescent alcohol exposure escalating adult drinking in some studies, though not in our hands. Therefore, we examined vimentin, an intermediate filament protein expressed in reactive astrocytes, and FluoroJade B (FJB), a marker for neuronal cell death, in a male rat model of adolescent intermittent alcohol exposure (AIE) as well as in AIE followed by free-choice alcohol drinking in adulthood. AIE consisted of 8 *i.p.* injections of 2 g/kg ethanol (20% w/v) or 0.9% saline (AIS) during postnatal day (PND) 30-43. At PND 44, half of the rats were sacrificed via transcardial perfusion (IP group; AIE *n*=8, AIS *n*=8) in order to assess the astrocyte response and cell death

immediately following AIE. On PND 87, 2 bottle choice (2BC) started for the remaining rats. Two bottles were placed in the home cage: one contained ethanol in water and the other contained only water. Every three days, rats were offered an increased concentration of EtOH (ranged 3% to 9%), and daily consumption from both bottles was recorded. As we have reported previously, AIE rats did not escalate voluntary alcohol drinking in adulthood compared to AIS. Following 2BC, rats were transcardially perfused on PND 112 (2BC group; AIE n=8, AIS n=8), and brain tissue was processed for histological measures of astrocyte reactivity (Vimentin) and cell death (FJB). Vimentin immunoreactive area (Vim+IR) was determined in the forceps minor of the corpus callosum using ImageJ (Fiji), while vimentin+ astrocytes were manually counted in the dorsal hippocampus. Likewise, FJB+ cells were manually counted in the hippocampus. Blood ethanol concentration for the AIE groups measured 154.6±13.9 mg/dL at 1 hr after the last injection. No FJB+ cells were detected in the hippocampus of any rat in the experiment. In the corpus callosum, two-way ANOVA revealed no main effects though a significant interaction (F(1, 26)=8.390, p=.0076), reflecting that AIE rats had a 33±0.02 % increase (p=0.03) in Vim+IR following *i.p.* injection that resolved even after 2BC drinking. In the hippocampus, there was no significant interaction, but there was a trend (p=.066) for a main effect of alcohol: fewer vimentin+ cells were counted in the alcohol groups regardless of treatment condition. Taken together, these results indicate that while no cell death was detected, adolescent alcohol exposure only induced modest changes in astrocyte reactivity in both adolescence and adulthood.

Disclosures: J. Wooden: None. **L. Peacoe:** None. **C. Anasooya Shaji:** None. **C. Chandler:** None. **M. Bardo:** None. **K. Nixon:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.04/J10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Reporter bioluminescence assay of TREM1 dimerization and TREM1/DAP12 interaction with a novel class of TREM1 inhibitors.

Authors: *N. FILIPPOVA[1], X. YANG[2], L. B. NABORS[3];
[1]Neurol., UAB, Birmingham, AL; [2]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL; [3]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: TREM1 (triggering receptor expressed on myeloid cells 1) is a valuable biomarker of neuroinflammation. Proinflammatory TREM1 receptors expressed on myeloid-derived cells are recently recognized as a new oncogenic target in cancer, including gliomas. They are established chemotherapeutic targets in neurodegenerative Parkinson's and Alzheimer's diseases, and they also contribute to stroke and sepsis severities. TREM1 activation requires ligand-dependent dimerization and TREM1/DAP12 interaction for receptor clustering and signal transduction. Here, we established the quantitative cell-based high throughput split-luciferase assays of

TREM1 dimerization and TREM1/DAP12 interaction that allow screening of the inhibitory compounds with quantitative dose-responses, IC50s, and specificity evaluation. The assays are based on the reconstitution of firefly luciferase activity during TREM1 dimerization or TREM1/DAP12 interaction leading to robust luminescence signal in the presence of luciferin. The following dox- inducible stable cell lines i) dox- inducible TREM1-Nluc plus dox- inducible TREM1-Cluc plus constant DAP12 co-expression, ii) dox- inducible TREM1-Nluc plus dox-inducible DAP12-Cluc co-expression, iii) dox-inducible TREM1-Cluc plus dox-inducible DAP12-Nluc co-expression, iv) dox- inducible DAP12-Nluc plus dox- inducible DAP12-Cluc co-expression, v) dox-inducible TREM2-Nluc plus dox-inducible DAP12-Cluc co-expression - were developed based on U251TEETON cell line. The ligand-dependent and independent SCHOOL TREM1 inhibitory peptides were utilized for assay validation. The TREM1 inductions in developed clones enhanced the LPS-induced IL6 release. Our pilot screen identified several new small compounds disrupting TREM1 dimerization and TREM1/DAP12 interaction. The potential compound mechanisms of action and binding sites in TREM1 and TREM1/DAP12 complexes were reviled using CB-Dock2 docking software. According to our knowledge, this is the first report providing a potential first-in-class pharmaceutical modulators of TREM1 clusterization and TREM1/DAP12 interaction.

Disclosures: **N. Filippova:** None. **X. Yang:** None. **L.B. Nabors:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.05/K1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS123084

Title: Interferon-gamma-producing T cells activate neurons and astrocytes prior to symptoms in a mouse model of multiple sclerosis

Authors: *S. M. O'NEIL, H. MIN, L. XU, D. N. CLARK, A. J. FILIANO;
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Abstract: Interferons (IFNs) are a key component of an organism’s response to viral infection and are strongly linked to autoimmune disorders, such as multiple sclerosis (MS). The impact IFNs play in the pathogenesis of MS is complex and likely depends on timing, location, and the cellular target. For example, it is generally thought that IFN-γ has a detrimental effect early in MS yet may play a more beneficial role as the disease progresses. Early in the disease, it is thought that IFN-γ and other cytokines produced by T cells in the meninges drive inflammation in the underlying cerebral cortex. How T cell-derived IFN-γ reaches the cortex, what CNS cell-types respond to IFN-γ, and the consequences of this CNS IFN stimulation are unknown. In this study, I show novel evidence that CNS antigen-specific T cells preferentially home to the

meninges, and induce a localized IFN-associated response in cortical and hippocampal neurons and astrocytes during the MS mouse model of experimental autoimmune encephalomyelitis (EAE). Moreover, this CNS IFN signaling can be observed in the pre-symptomatic stages of the disease and in the absence of blood-brain barrier (BBB) breakdown and white matter lesions. Chronologically, neurons detect IFN signaling prior to astrocytes, suggesting a mechanism by which neurons directly respond to peripheral T cell-derived IFN production. Indeed, I show these IFN-detecting neurons extend processes to the pia mater (cortical neurons) or the lateral ventricles (hippocampal neurons). These IFN-responsive neurons increase in density as EAE progresses, and astrocytes located along the processes of these neurons begin to detect IFNs toward the onset of clinical symptoms. Taken together, these data show neurons in the cortex and hippocampus detect peripherally derived IFNs during EAE and propagate IFN signaling within the CNS even prior to the onset of clinical symptoms and in the absence of BBB breakdown and white matter lesions.

Disclosures: S.M. O'Neil: None. **H. Min:** None. **L. Xu:** None. **D.N. Clark:** None. **A.J. Filiano:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.06/K2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: JIT768 ICTS funding program
HA Innovator Award 2022
PR221066 DOD

Title: Cerebrospinal fluid-based extracellular vesicle signaling and related T-cell activation mediate the pathogenesis of posthemorrhagic hydrocephalus

Authors: *M. GARCIA BONILLA[1], D. GILES[1], A. ISAACS[2], D. MORALES[1], K. SHUMILOV[1], E. KIZILTUG[3], J. P. MCALLISTER, II[1], K. T. KAHLE[4], D. LIMBRICK, Jr[5]; [1]Neurosurg., Washington Univ. in St Louis, St Louis, MO; [2]Neurolog. Surgery, Vanderbilt Univ. Med. Ctr., Nashville, TN; [3]Neurosurg., Yale Univ., New Haven, CT; [4]Neurosurg., Massachusetts Gen. Hosp., Boston, MA; [5]Neurosurg., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: *Introduction*: Intraventricular hemorrhage (IVH) is the most common, severe neurological complication of preterm birth and is closely associated with ventricular/subventricular zone (V/SVZ) disruption and post-hemorrhagic hydrocephalus (PHH). IVH-related inflammation has been implicated in the pathogenesis of PHH but is poorly characterized. In the current study, we hypothesize that cerebrospinal fluid (CSF)-based extracellular vesicles (EVs) mediate the pathogenesis of PHH CSF T-cell activation.*Methods*: EV and cell profiles from CSF of human neonates with PHH were compared to IVH grade 1-2,

congenital hydrocephalus (CH), and controls (no known neurological injury). EVs were isolated and analyzed by mass spectrometry-based high-throughput proteomics. Cells were analyzed by single-cell RNA sequencing and flow cytometry. T-cell activation after EV exposure was studied *in vitro* by bulk RNA sequencing, flow cytometry, and ELISA; and in post-mortem brain samples by immunofluorescence.*Results*: PHH CSF samples contained a significant increase in EV pro-inflammatory proteins compared to control and CH. Furthermore, robust populations of activated T cells and myeloid cells were detected in the CSF in PHH. EVs activated T cells to produce the pro-inflammatory interleukins IL1β, IL6, and tumor necrosis factor-alpha (TNFα) through the nuclear factor-κB (Nf-kB) pathway in PHH. Finally, T-cell recruitment and the same cytokine production were detected in the choroid plexus of post-mortem IVH/PHH samples.*Conclusion*: Our data uncover a novel contribution of EVs and T cells to the pathogenesis of PHH. We demonstrated a new role for EV signaling in T cell activation through Nf-kB pathway, and identified several inflammatory molecules that could be targeted to treat PHH. Defining EV and cell profiling will lead to new pharmacological therapies to improve outcomes for patients with PHH.

Disclosures: M. Garcia Bonilla: None. **D. Giles:** None. **A. Isaacs:** None. **D. Morales:** None. **K. Shumilov:** None. **E. Kiziltug:** None. **J.P. McAllister:** None. **K.T. Kahle:** None. **D. Limbrick:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.07/K3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Emil Aaltonen Foundation
The Finnish Medical Foundation
Päivikki and Sakari Sohlberg Foundation
The Finnish Brain Foundation
Sigrid Jusélius Foundation

Title: A brief cytokine independent switch in cortical activity marks the onset of sickness behavior triggered by acute peripheral inflammation

Authors: *S. N. KURKI[1], T. ALA-KURIKKA[1], A. LIPPONEN[2], A. POSPELOV[1], T. ROLOVA[1], J. E. KOISTINAHO[1], J. T. VOIPIO[3], K. KAILA[1];
[1]Univ. of Helsinki, Helsinki, Finland; [2]Univ. of Jyväskylä, Jyväskylä, Finland; [3]Univ. of Helsinki, Dept. of Biosciences, Univ. of Helsinki, Helsinki, Finland

Abstract: Systemic inflammation triggers protective as well as pro-inflammatory responses in the brain based on neuronal and/or cytokine signaling, and it associates with acutely and protractedly disrupted cognition. However, the multiple mechanisms underlying the peripheral-

central inflammatory signaling are still not fully characterized. We used intraperitoneal (i.p.) injection of lipopolysaccharide (LPS) in freely moving mice with chronically implanted electrodes for recording of local field potentials (LFP) and electrocorticography (ECoG) in the hippocampus and neocortex, respectively. We show here that a sudden switch in the mode of network activity occurred in both areas starting at 10-15 minutes after the LPS injection, simultaneously with a robust change from exploration to sickness behavior. This switch in cortical mode commenced before any elevations in pro-inflammatory cytokines IL-1β, TNFα, CCL2 or IL-6 were detected in brain tissue. Thereafter, this mode dominated cortical activity for the recording period of three hours, except for a partial and transient recovery around 40 minutes post-LPS. These effects were closely paralleled by changes in ECoG spectral entropy. Continuous recordings for up to 72 hours showed a protracted attenuation in hippocampal activity, while neocortical activity recovered after 48 hours. The acute sickness behavior recovered by 72 hours post-LPS. Notably, urethane (1.3 mg/kg) administered prior to LPS blocked the early effect of LPS on cortical activity. However, experiments under urethane-anesthesia which was started 24 hours post-LPS (with neuroinflammation fully developed before application of urethane) showed that both theta-supratheta and fast gamma CA1 activity were reduced, DG delta activity was increased, and sharp-wave ripples were abolished. Finally, we observed that experimental compensation of inflammation-induced hypothermia 24-48 hours post-LPS promoted seizures and status epilepticus; and that LPS decreased the threshold of kainate-provoked seizures beyond the duration of acute sickness behavior indicating post-acute inflammatory hyperexcitability. Taken together, the strikingly fast development and initial independence of brain cytokines of the LPS-induced cortical mode, its spectral characteristics and simultaneity in hippocampus and neocortex, as well as inhibition by pre-applied urethane, strongly suggest that the underlying mechanisms are based on activation of the afferent vagus nerve and its mainly cholinergic ascending projections to higher brain areas.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.08/K4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: HK GRC grant 17101020
HK GRC grant 17100622
Hong Kong PhD Fellowship (HKPF)
HKU Presidential Scholarship (HKUPS)

Title: Evaluation of macrophage polarization and infiltration in a murine model of perioperative neurocognitive disorders

Authors: *K. I. Y. OH[1,2], M. CHU[1,2], G. T. C. WONG[1], R. C. C. CHANG[2,3];
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Abstract: Systemic inflammation leads macrophage polarization and infiltration with its metabolic reprogramming, and the prolonged inflammation can cause neurocognitive disorders. In this study, the pathogenic levels were evaluated using a murine model of perioperative neurocognitive disorders. To set up the murine model, sevoflurane only (SO) or laparotomy with sevoflurane (LS) were operated in the C57BL/6J (male, 4-6 months old) mice. The operations were conducted either one (1x) or twice (2x). Two weeks after the final operation, the mice were euthanized, and the samples were collected. Open field and novel object recognition tests were conducted for 3 days before euthanizing the mice. SO/LS group mice showed significantly decreased global activity, and the latency against new object was significantly increased in 2x LS mice compared to 1x LS mice (Day 3). In the qRT-PCR data, pro-inflammatory cytokines (IL6 and TNFα) were increased, and anti-inflammatory markers (Retnla and CD206) were decreased in the hippocampus of SO/LS. Single cells were isolated from hippocampus and stained with the specific markers (CD45, CD11b, TMEM119, CD68, and CCR2), and the macrophages ($CD45^{+}CD11b^{high}$) and microglia ($CD45^{+}CD11b^{low}$) were analyzed by flow cytometry and clustered by tSNE. Mean fluorescence intensity of CD86 and CCR2 were evaluated from the $CCR2^{low}$ and $CCR2^{high}$ microglia. Macrophages/microglia were sorted from peritoneal lavage and hippocampus, and the sorted cells were observed under microscope (Carl Zeiss LSM 780, 40x oil lens) and DNA was extracted to measure the mtDNA (mitochondrial DNA) copy number. In this study, the activated macrophages/microglia were detected in periphery and brain of the SO/LS, microglia of 1x SO group showed relatively higher percentage of $CCR2^{+}$ and $CD86^{+}$ cells, meanwhile most of the microglia in other groups expressed lower level of CCR2. In addition, mtDNA copy numbers were decreased in the macrophages/microglia in LS compared to those in SO. In conclusion, both SO and LS induce systemic inflammation with upregulating of the pro-inflammatory factors with the different extents between the experimental groups. Macrophages have possibly infiltrated into hippocampus in LS group, with attenuation of mitochondria in macrophages and microglia.

Disclosures: K.I.Y. Oh: None. **M. Chu:** None. **G.T.C. Wong:** None. **R.C.C. Chang:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.09/K5

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant F30HD108912
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NIH Grant P30ES005022

NJ Governor's Council for Medical Research and Treatment of Autism
CAUT20AFP004

Title: Caesarean delivery alters postnatal brain and gut microbiome development in a mouse model of autism.

Authors: *J. K. LESSING[1,2], X. ZHOU[1], H. SUN[2], W. MOHAMAD[2], A. DEUTSCH[2], M. G. DOMINGUEZ-BELLO[2], E. DICICCO-BLOOM[1];
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Abstract: Neurodevelopmental diseases – including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and intellectual disability - are thought to be caused by a combination of genetic susceptibility and environmental triggers. Caesarean-section delivery (CS) encompasses many environmental changes, including altered microbiome, hormonal environment, and drug exposures, which may secondarily affect the brain. Epidemiological studies correlate CS to a 33% increased risk of developing autism and a 17% increased risk of ADHD. We designed a system in a genetic model of neurodevelopmental susceptibility to study effects of CS on neurodevelopment and investigate gene x environment interactions. We expect changes in hippocampus at P7 are associated with changes in microbiome. In humans, the 16p11.2 copy number variant (CNV) is responsible for approximately 1% of autism cases, and carriers have a 40-fold risk of autism, 4-fold risk of ADHD, and 60-fold risk of intellectual disability. This heterozygous CNV is conserved in mice. These mice exhibit behavioral phenotypes and cytoarchitectural abnormalities associated with autism, including: restrictive, stereotyped, and non-coordinated motor patterns, hyperactivity, and altered brain volumes. In our current study, timed-pregnant dams were allowed to give birth vaginally (control) or underwent terminal CS on gestational day 19. Pups from both groups, including WT and $16p^{+/-}$, were cross-fostered by dams giving birth in the previous 24-hours. Following sacrifice on P7, we isolated hippocampus for transcriptomic analysis. Principle Component Analyses show the transcriptome segregates based on delivery status. Pathway analysis shows 17 KEGG pathways were consistently altered in C-section mice across both genotype and sex. Out of 16 pathways significantly downregulated in CS mice, 11 may alter brain development: synaptic pathways (glutamatergic, GABAergic, cholinergic, dopaminergic), signaling (oxytocin, endocannabinoid), addiction (morphine, nicotine), synaptic vesicle cycle, long-term potentiation, circadian entrainment. The one up-regulated KEGG pathway in CS pups is herpes simplex virus 1 infection. Additionally, following sacrifice on P7 and P21, we isolated colon, cecum, and ileum contents for 16S microbiome sequencing. Preliminary data from P21 mice show birth mode significantly altered the microbial communities in the colon ($p < 0.01$), cecum ($p < 0.01$) and ileum ($p < 0.05$). Future investigation will determine if these microbial changes extend to the earlier P7 timepoint.

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

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.10/K6

Topic: C.06. Neuromuscular Diseases

Support: Aust. Nat. Health & Med Res Council (NHMRC), Development Grant, APP1179074
MDA USA grant (https://doi.org/10.55762/pc.gr.157039)
CS and SY are supported by UQ PhD Scholarships

Title: Targeting prostaglandin D2 synthase for the treatment of inflammatory neuromotor associated diseases

Authors: *C.-L. SHEREMETA[1,2,3], S. YARLAGADDA[3], D. KONG[2], P. G. NOAKES[3], M. L. SMYTHE[2];
[1]The Univ. of Queensland, Brisbane, Australia; [2]Inst. for Mol. Biosci., Brisbane, Australia; [3]Sch. of Biomed. Sci., Brisbane, Australia

Abstract: Prostaglandin D2 synthase (PGDS) has proinflammatory effects in various neuromotor and neuromuscular diseases, like multiple sclerosis, amyotrophic lateral sclerosis, and muscular dystrophy, where its product prostaglandin D2 (PGD2) has a role in regulating some adverse disease characteristics. Specifically, PGD2 metabolites are clinically upregulated in these inflammatory diseases, as well as in vivo murine models. Currently, pharmacological agents available for the treatment of these diseases are limited. Here, we describe the optimisation of our lead PGDS inhibitor, PK007 through our structure activity relationship database. Assayed through PGDS fluorescent polarisation-based inhibitor screening assays (Cayman Chemical, n=7), potency of our compounds was determined. Novel inhibitors CLS122 (IC50:0.14µM) and CLS210 (IC50:0.25µM) exhibited approximately an 11- and 6- fold increase in potency compared to PK007 (IC50:1.58µM), respectively. These potencies were more than 200-fold more potent than literature reported PGDS inhibitor, HQL-79 (IC50:50µM). Next, we tested their therapeutic potential through a series of selected in vitro cell-based stability assays (human and mouse hepatocyte and liver microsomes, n=1). CLS122 had comparable stability in both assays to PK007 (T1/2>145min), whilst CLS210 had reduced stability (T1/2:11min). To identify this metabolic weak point in CLS210, we conducted a metabolite identification study (mouse liver microsomes, n=1), which will aid in the further optimisation of this compound. PGD2 stimulates the recruitment and activation of various immune cells; microglia are a main source of PGD2 within the CNS. To observe if our therapeutics diminish inflammation through inactivation of these cells, we are currently utilising in vitro inflammatory models, by treating LPS-stimulated microglia (murine BV2) with our PGDS inhibitors to quantify proinflammatory cytokines via qPCR. It is expected there will be a marked decrease in these inflammatory factors compared to untreated cells, with similar cytokine levels compared to cells treated with a non-steroidal anti-inflammatory drug (Indomethacin).
Overall, we have optimised our lead compound PK007 and successfully compared to two newly synthesised lead compounds (CLS122 and CLS210) for further modification aimed at stabilizing the bioactive tail group to retain potency and increase metabolic stability. These improvements

will allow us to assess and choose the most therapeutically effective PGD2 inhibitor for proof-of-concept pre-clinical studies, in the treatment of inflammatory neuromuscular - neuromotor diseases.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.11/K7

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

Support: 4R00NS 11410703

Title: Characterization of Cell Types Required for Immune-Brain Communication

Authors: *M. S. SWAROVSKI, J. A. OSTERHOUT;
Univ. of Utah, Salt Lake City, UT

Abstract: During an acute infection the body exhibits a set of highly stereotyped symptoms including fever, loss of appetite, fatigue, altered sleep and social interactions. A key open question concerns how the immune system communicates with the brain to generate these symptoms. We hypothesize that a major hub of communication between the periphery and the brain are circumventricular organs (CVOs). These structures are vascularized with fenestrated blood vessels that lack the usual tight junctions within the blood brain barrier and have been reported to express immune receptors. Here we aim to uncover the unique non-neuronal cell types that facilitate the communication between the peripheral immune system and brain CVOs following various sources of inflammation. We utilized single nucleus RNA-sequencing of immune-activated CVO regions to molecularly characterize cell types responding to acute inflammation. We determined that inflammation increased expression of key immune genes in a subset of non-neuronal cell populations within several CVOs, suggesting direct signaling mechanisms between the peripheral immune system and the brain following bacterial and viral mediated inflammation. Together, these results are essential for revealing the biological relevance of the cellular networks that comprise CVOs and deciphering the cellular and molecular mechanisms of immune-brain communication.

Disclosures: M.S. Swarovski: None. **J.A. Osterhout:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.12/K8

Topic: B.09. Glial Mechanisms

Support: HK110-165

Title: The effects of alcohol on neuroinflammation in rats

Authors: *J.-Y. WANG[1], C.-L. CHEN[2], S.-Y. CHEN[1], C.-H. YANG[3], S.-N. YANG[3];
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Abstract: Alcohol (EtOH) is considered to be one of the most commonly abused chemical. Excessive alcohol consumption induces neurological function disorder including change of neuroinflammatory response and impairment in learning and memory function. Neuroinflammation is known as an important factor in neurodegeneration, and the activation of glial cells (including astrocytes and microglial cells) may play the key role. Alzheimer's disease (AD) is the most common neurodegenerative disease. It is associated with neuroinflammatory response, too. Evidence indicated that ethanol exposure induced microglial over activation to release inflammatory mediators including tumor necrosis factor (TNF)-α and nitric oxide (NO) and decreased the number of neurons in mice brain. However, some data indicated that the microglial activation was not positive correlation to neuroinflammation in EtOH-induced neurodegeneration. Even though glial cells are very important constituents in the brain, but the results of investigation of EtOH in glial cells are not clear. In this study, we wanted to estimate the role of glial cells in neuroinflammation following alcohol exposure in rats. Male SD rats fed with various concentration of alcohol for 1 week (Day 1 and 2: 1 %; Day 3 and 4: 5 %; Day 5, 6 and 7: 10 % alcohol). The diet of rats was restricted in order to decrease 20 % body weight. Then we started operating the behavioral experiment and estimated the memory functions by 8 arm maze. Rats were sacrificed after about 1 month and prepared brain section for immunocytostaining. The results of immunocytostaining of brain slices revealed that the number of neuron and astrocyte were decreased significantly in prefrontal cortex and hippocampus (CA1); however, the activation of microglial cells was increased significantly in alcohol treatment group. Furthermore, the expression of TNF-α, iNOS and NFκB were significant increased. We suggested that alcohol will impair the neuron and astrocyte, and alcohol will induce the activation of microglial cells to release inflammatory mediators.

Disclosures: **J. Wang:** None. **C. Chen:** None. **S. Chen:** None. **C. Yang:** None. **S. Yang:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.13/K9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NIAAA R01AA02379
NIGMS T32GM8339, T32GM135141
NCATS 1TL1TR003019

Title: Ethanol-induced Neuroimmune Dysregulation in a Human Stem Cell-derived Neuron, Astrocyte, and Microglia Tri-culture Model

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Abstract: Alcohol use disorders (AUDs) are escalating health concerns affecting a substantial population worldwide and heighten the risk of developing cognitive impairments and alcohol-associated dementia. While the precise cellular mechanisms of this pathology remain elusive, developing evidence points towards neuroinflammation as a critical player in AUD-related dementia. To investigate how alcohol/ethanol dysregulates neuroimmune interactions in a human context, we constructed a neural tri-culture model derived from human induced pluripotent stem cells (hiPSCs), comprising neurons, astrocytes, and microglia. We used a one-week intermittent ethanol exposure paradigm with biologically relevant ethanol concentrations of 20 mM, 40 mM, or 75 mM to mimic patients with AUDs. Ethanol exposure caused microglial activation both in monoculture and tri-culture, evidenced by increased inflammatory gene transcripts and CD68 expression. Interestingly, in monoculture, we observed reduced microglial phagocytic function following ethanol exposure. Notably, in tri-culture ethanol led to dose-dependent activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome innate immune pathway and subsequent Interleukin-1β (IL-1β) induction. Bulk RNA sequencing of tri-cultures revealed robust dose-dependent changes in differentially expressed genes related to pro/anti-inflammatory signaling, innate immune pathways, and dementia disease-risk genes. Our ongoing investigation aims to understand how ethanol-induced neuroinflammation and microglial activation impact neuronal functionality, encompassing intrinsic physiological properties and synaptic transmission. Deciphering the molecular and cellular mechanisms underpinning ethanol-related neuroimmune dysregulation within a human context promises to shed light on the etiology of AUD and AUD-associated dementia, potentially driving the development of effective therapeutic strategies.

Disclosures: A.J. Boreland: None. **Y. Abbo:** None. **A.C. Stillitano:** None. **S. Zhang:** None. **J. Duan:** None. **X. Li:** None. **R. Gabriel:** None. **R.P. Hart:** None. **Z.P. Pang:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.14/K10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Unveiling the interplay of CXCR3, ISG15, and DDX58 pathways in multiple sclerosis inflammatory milieu

Authors: *M. CABRERA SALAIZA[1], K. ADIL AHMAD[1], **A. RUIZ RAMÍREZ**[2], L. ÁLVAREZ PALAZUELOS[2];
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Abstract: Multiple sclerosis (MS) is a chronic inflammatory disease, the cells reported as mainly affected in the description of pathological findings in patients with MS are the oligodendrocyte (OLG) that seem more susceptible than the rest of the CNS cells. This study aimed to evaluate the differently expressed genes (DEG) and the affected pathways between induced pluripotent stem cells (iPSCs) from peripheral blood mononuclear cells derived from stable and progressive MS patients and then further differentiated them into oligodendrocyte lineage cells exposed to either homeostatic or inflammatory conditions via sustained exposure to low-dose interferon gamma (IFNγ) . Material/Methods: The gene expression dataset GSE147315 was downloaded from the GEO database, and DEG was obtained. The highest upregulated genes with a log2 fold change threshold of 7 were examined in the String platform for the protein-protein interaction (PPI) network, with a Confidence≥0.4. Results: The main genes up-regulated with log2 fold of 7 were identified and analyzed, determining a final network of 17 nodes, 55 edges, and a PPI enrichment p-value of < 1.0e-16. The main intervening pathways were CXCR3 chemokine receptor binding, Interferon alpha/beta signaling and ISG15- protein conjugation, Interferon alpha/beta signaling, and negative regulators of DDX58/ IFIH1 signaling. Conclusions/Discussion: The participation of IFNγ in peripheral blood from MS patients and the localization around the MS lesion has been well documented so that it can affect multiple cells. In this study, we found the participation of CXCR3, a critical factor that interferes with cell differentiation, as in early CD8 T cells. To our knowledge, only CXCR2 has been related to the OPC environment during neuroinflammation, which is necessary to inhibit apoptosis. ISG15, the other disturbed element, can be secreted by microglia cells when treated with IFNγ and promotes microglial activation. ISG15 is also involved in the maturation process, as in bone cells, when up-regulated by interferon-β can negatively intervene in osteoclastogenesis. RIG-I o DExD/H-box helicasa 58 (DDX58) similarly affects differentiation, acting as a hub regulator between RNA and proteins in hematopoiesis during acute promyelocytic leukemia cell differentiation. In this study, we found three important pathways previously reported as key players in cell differentiation in other tissues that could explain the inhibition of the development of the oligo lineage exposed to low chronic doses of IFNγ seen in MS models and reported by other groups.

Disclosures: M. Cabrera Salaiza: None. **K. Adil Ahmad:** None. **A. Ruiz Ramírez:** None. **L. Álvarez Palazuelos:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.15/L1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Chitinase-induced activation of monocyte-derived macrophages

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Abstract: Abstract: Neuroinflammation is widely regarded as a contributing factor to the pathogenesis and disease progression of Amyotrophic Lateral Sclerosis (ALS) as well as other neurodegenerative disorders. This inflammatory response can be measured through a host of protein-based biomarkers that are secreted into body fluids or using immunohistochemistry for activated glia in post-mortem tissue. Chitinase proteins, specifically, chitotriosidase-1 (Chit-1) and chitinase-3-like protein 1 (CHI3L1) are a group of proteins that have been investigated as biomarkers of neuroinflammation in ALS. Chitinase proteins have also been implicated in neuroinflammatory responses in other neurodegenerative disorders, including frontotemporal dementia (FTD) and Alzheimer's Disease (AD). Studies from our group as well as others have shown CHI3L1 and Chit-1 to be expressed predominantly in a subset of activated astrocytes and microglia, respectively. Although it has been shown that chitinases are produced by glial cells in the central nervous system, it is still unknown whether chitinase proteins are associated with a pro- or anti-inflammatory glial cell phenotype. We propose that Chit-1 and CHI3L1 are pro-inflammatory in nature and will exert a cell specific effect on monocyte-derived macrophages. Using an in vitro model system, we will test the hypothesis that Chit-1 and CHI3L1 activate monocyte-derived macrophages via the JAK/STAT6 pathway. Studying the effect of secreted chitinase proteins on glial cell profiles will further our understanding of neuroinflammation as it pertains to neurodegeneration and identify new targets for therapy.

Disclosures: C. Tran: None. **R. Bowser:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); nVector.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.16/L2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Hyperaloric diet consumption induces inflammaging phenotype in the hippocampus of male Wistar rat

Authors: *G. GONZALEZ LÓPEZ, S. TREVIÑO, A. DÍAZ;
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Abstract: Metabolic disorders have become a global health problem. Recently, it has been established a relationship between metabolic diseases and neuroinflammation. Active microglial cells are a hallmark of neuroinflammatory disorders, modulating pro- and anti-inflammatory cytokine secretion. It is important to note that the microglia can reprogram in M1 or M2 in response to different conditions or stimuli. Thus, imbalances in the inflammation of M1 microglia have been associated with neuroinflammatory and neurodegenerative diseases. However, the mechanisms regulating the M1 and M2 programming are unknown. Therefore, we aimed to evaluate the effect of metabolic syndrome (MetS) on the pro- and anti-inflammatory microglia response in the hippocampus of the male Wistar rat. Male Wistar rats (N=20, 100g of weight) were used and randomly divided into two groups. The group that consumed a regular diet (NCD) and a hypercaloric diet group (HCD) were fed for 3 months. At the end of the experimental time, blood samples were taken to determine the oral glucose tolerance, insulin response, triglycerides, free fatty acids, total cholesterol, HDL, LDL, and VLDL, as well as HOMA-IR, IRCV, and Matsuda-DeFronzo indices. Additionally, we quantified the interleukins IL-1β, IL-6, IL-17, IL-10, IL-4, TNF-α, and TGF-β, and immunolabeling to identify M1 (CD16) and M2 phenotype (CD206). Our results demonstrate that HCD consumption induces MetS. In addition, MetS generated inflammaging, causing an increase in the number of microglia cells with the M1 phenotype. Together, these results suggest that MetS contributes to the development of the neuroinflammatory-degenerative process.

Disclosures: G. Gonzalez López: None. **S. Treviño:** None. **A. Díaz:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.17/L3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: 2d and 3d tri-culture systems for investigation of cellular interaction among neurons, astrocytes, and microglia

Authors: *H. KOBAYASHI, H. KATO, S. ENDOH-YAMAGAMI;
Bio Sci. & Engin. Labs., FUJIFILM Corp., Kanagawa, Japan

Abstract: The central nervous system is composed of two main classes of cells: neurons and glial cells. Nowadays, it is widely recognized that interaction between neurons and glial cells is deeply involved in brain function and pathogenesis. For better understanding of the cellular interaction between neurons and glia, new multicellular culture systems are required. Therefore, we established 2D and 3D tri-culture systems using hiPSC-derived neurons, astrocytes, and microglia to investigate the relationship between neurons and glia in both homeostatic and

pathological conditions. In this study, a 2D tri-culture system was constructed using hiPSC-derived neurons, astrocytes, and microglia. While microglia showed amoeboid morphology in monoculture, branched processes were detected in the tri-culture system. With LPS stimulation, microglia in the tri-culture system showed morphological changes from branched to amoeboid shape in a time-dependent manner. Furthermore, it was revealed that activated microglia interacted with other cells through cytokines in our 2D tri-culture system. Next, we constructed a 3D tri-culture system. Microglia in the 3D tri-culture system also showed branched morphology. Now, we are trying to evaluate cellular interaction of neurons and glial cells in the 3D tri-culture system. Moreover, both 2D and 3D tri-culture systems were able to detect calcium oscillation, and we are evaluating neuronal function in various conditions. Microglia in our tri-culture system showed branched shape, which suggests that microglia are more homeostatic state compared with microglia in monoculture. In addition, it was confirmed that activated microglia transferred the signal to other cells through cytokines. Therefore, our tri-culture system can be useful to study cellular interaction for brain function and neurological disorders.

Disclosures: **H. Kobayashi:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **H. Kato:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Funded by Concept Life Sciences Ltd

Title: Design, synthesis, and biological characterisation of a novel small molecule inhibitor of microglial proinflammatory regulator HuR

Authors: ***E. MALAVASI**[1], C. COLVIN[1], B. HALL[1], C. COOK[1], P. BEAGLEY[2], T. PESNOT[2], M. BINGHAM[2];
[1]Concept Life Sci., Edinburgh, United Kingdom; [2]Concept Life Sci., Chapel-en-le-Frith, United Kingdom

Abstract: Chronic activation of microglia is a common feature and recognised pathological driver of many neurodegenerative diseases, including Multiple Sclerosis and Alzheimer's disease. Activated microglia drive inflammation by producing and releasing inflammatory mediators such as cytokines and chemokines. Expression of many of these inflammatory factors by microglia is regulated at the post-transcriptional level via adenine- and uridine-rich elements (ARE) located in the 3' untranslated region of their mRNA. Human antigen R (HuR) is a RNA binding protein that, by interacting with AREs, stabilises and promotes the translation of multiple inflammatory mediators in microglia. In resting microglia, HuR is predominantly

localised in the nucleus, but upon microglial activation, it translocates to the cytoplasm, where it drives mRNA stability and translation. Homodimerisation of HuR is necessary for nuclear export. Thus, small molecules that can block this process have the potential to inhibit glial-mediated inflammatory processes in the brain, offering a new therapeutic avenue for neurodegenerative diseases. SRI-42127 has recently been reported as a low µM inhibitor of HuR homodimerization and cytoplasmic translocation, however it has poor physicochemical properties such as solubility, which has limited its use to a tool compound for studying the biology of HuR. In the present study, we describe CLS-2802282, a novel analogue of SRI-42127 designed to have a differentiated physicochemical and pharmacokinetic profile, and test it against SRI-42127 for its ability to suppress pro-inflammatory responses in microglia. To assess the biological activity of this novel molecule, primary microglia are isolated from Sprague Dawley rat neonate brains and stimulated with lipopolysaccharide (LPS) to induce pro-inflammatory activation, in the presence or absence of increasing concentrations of CLS-2802282 or SRI-42127. After 24 hours of treatment, the supernatants are collected, and levels of pro-inflammatory cytokines analysed by multiplex ELISA. Concomitantly, cells are fixed and stained for microglial marker Iba1, pro-inflammatory polarisation marker iNOS and HuR. The effect of CLS-2802282 on HuR cytoplasmic translocation and cytokine secretion upon microglial pro-inflammatory stimulation is presented and discussed.

Disclosures: **E. Malavasi:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **C. Colvin:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **B. Hall:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **C. Cook:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **P. Beagley:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **T. Pesnot:** A. Employment/Salary (full or part-time):; Concept Life Sciences. **M. Bingham:** A. Employment/Salary (full or part-time):; Concept Life Sciences.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.19/L4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: PM30 GM145646 NIH NIGMS
NIGMS GM103440

Title: Accumulation of C1qa Found within the Perineuronal Net

Authors: *M. DEFERRARI, S. PIERAUT;
Univ. of Nevada, Reno, NV

Abstract: Accumulation of C1qa Found within the Perineuronal Net
Marika DeFerrari[1,] and Simon Pieraut[1]. [1]Department of Biology, University of Nevada Reno, Reno, NV

C1qa, a complement molecule primarily recognized for its involvement in the immune system, has recently garnered attention for its central role in mediating synaptic pruning through phagocytosis by microglia. Microglia, the primary source of C1qa in the brain, are also actively involved in the remodeling and phagocytosis of the perineuronal net (PNN), a specialized extracellular matrix composed of proteoglycans. The PNN plays a key role in regulating brain plasticity, cell-cell signaling, and protecting against cytotoxicity. Disruptions in the PNN surrounding Parvalbumin-expressing interneurons (PV-Ins) have been implicated as risk factors in various brain disorders, including Autism, Schizophrenia, Alzheimer's, and Epilepsy. Although microglia appear central for the phagocytosis of both PNN and synapses, a possible link between the two has not been investigated. In this study, we present novel data demonstrating the accumulation of C1qa within the PNN and propose a model to explain C1qa binding to the matrix. Surprisingly, our findings indicate that C1qa is not essential for PNN formation or the phagocytosis of the PNN by microglia. Based on our observations, we propose that the preferential binding of C1qa to the PNN contributes to the protection of synapses embedded within this matrix. Additionally, we observed a higher presence of C1qa within somatic inhibitory synapses in PV neurons lacking the PNN. These findings provide valuable insights into the intricate interplay between the PNN, C1qa, and synapse maintenance, suggesting a potential novel mechanism underlying synapse protection. Understanding the molecular mechanisms involved in these processes holds significant implications for unraveling the pathophysiology of brain disorders associated with PNN dysfunction and may pave the way for targeted therapeutic interventions.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

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Program #/Poster #: PSTR076.20/L5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01N5112350
R01N5112308

Title: C-c motif chemokine ligand 2 (ccl2)/ c-c motif chemokine receptor 2 (ccr2) signaling axis is required for lps-induced m1 pro-inflammatory macrophage differentiation.

Authors: *F. PAREDES[1,2], A. KAPUR[2], R. DINGLEDINE[2], N. H. VARVEL[2];
[1]Emory Univ., Decatur, GA; [2]Pharmacol., Emory Univ., Atlanta, GA

Abstract: Monocytes play a crucial role in the inflammatory response and tissue repair by differentiating into macrophages. Macrophages exhibit various phenotypes, including non-activated (M0), pro-inflammatory (M1), and anti-inflammatory (M2) types. Previous work from our group revealed that genetic knockout of *Ccr2*, or Ccr2 antagonism, mitigated the adverse

effects of status epilepticus. Targeting Ccr2 reduced pro-inflammatory monocyte recruitment to the inflamed brain. However, our previous findings do not rule out that blocking Ccr2/Ccl2 signaling might modulate inflammation beyond monocyte recruitment. Therefore, we asked if Ccr2 signaling promotes a pro-inflammatory phenotype in monocytes. Recombinant Ccl2 induced the expression of the pro-inflammatory cytokines IL6 and IL1B and increased the macrophage marker CD68 in the LPS-stimulated monocyte cell line, THP1. However, the anti-inflammatory cytokine IL10 expression remained unaffected. Additionally, Ccl2 caused upregulation of the M1 macrophage marker HLA-DR and downregulation of the M2 marker CD206, indicating that Ccl2 has pro-inflammatory functions on monocytes, promoting the M1 phenotype and suppressing M2. Ccr2 antagonism with a small molecule, or silencing Ccr2 with siRNA, attenuated the Ccl2-induced expression of IL6, IL1B, HLA-DR, and CD68. These findings indicate that the Ccr2/Ccl2 pathway is important for establishing the pro-inflammatory phenotype in monocytes and macrophage M1 polarization. Ccl2 stimulation in monocytes increased the phosphorylation of NF-κB and STAT3. Ccr2 antagonism inhibited the phosphorylation of both, indicating that Ccl2/Ccr2 axis promotes the induction of the NF-κB and STAT3 pathways. NF-κB or STAT3 inhibition reversed the expression of the pro-inflammatory cytokines IL6 and IL1-b. Still, only the inhibition of NF-κB reversed the expression of the differentiation markers CD68 and HLA-DR, indicating that NF-κB activation but not STAT3 is essential for promoting the M1 phenotype. We employed a model for M0, M1, and M2 phenotypes to investigate macrophage polarization further. Loss of function of Ccr2 blocks the induction of the M1 but does not affect the induction of the M2 phenotype. This indicates that CCR2 is required for macrophage polarization towards the M1 phenotype but not the M2 phenotype. Our findings highlight the essential role of Ccr2/Ccl2 signaling in monocyte differentiation and M1 phenotype polarization through the NF-κB pathway. These data provide insights into the regulatory mechanisms underlying macrophage phenotypic plasticity and offer a novel interpretation of the beneficial Ccr2 modulation after status epilepticus.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

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Program #/Poster #: PSTR076.21/L6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MOST 111-2314-B-303 -029 -

Title: Therapeutic Potential of Urocortin by Mitigating of Mitochondrial Dysfunction in Severe Intracerebral Hemorrhage-Hematoma Aspiration Model

Authors: *H.-K. LIEW[1], W.-F. HU[4], S.-T. TSAI[2], C.-Y. PANG[3];
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Abstract: Objective: Severe intracerebral hemorrhage (ICH) is a life-threatening condition characterized by hematoma compression, increased intracranial pressure, cerebral edema, blood-brain barrier disruption, neuroinflammation, and neuronal death. Surgical evacuation of the hematoma can provide therapeutic benefits, but complete evacuation is often challenging due to the risk of re-bleeding and technical limitations. The remaining blood clot and lysis will trigger a cascade of chemical reactions, releasing a variety of harmful substances, including heme, hemoglobulin, iron, and thrombin, causing excessive oxidative stress and neuroinflammation. In this study, using our newly established rat model of severe intracerebral hemorrhage that allows hematoma aspiration, we aimed to evaluate the therapeutic efficacy of intralesional administration of urocortin, a potent anti-inflammatory neuropeptide. Methods: Severe ICH with hematoma aspiration was induced in rats by microinjection of collagenase (0.6 U in 3 μl saline) into the striatum, followed by hematoma aspiration 6 hours after ICH induction. Urocortin was administered intralesionally after hematoma aspiration. Oxidative stress and mitochondrial dysfunction were assessed by measuring protein carbonyl and ATP levels, respectively. Brain hematoma volume and midline shift were assessed by 7T MRI. Neurological severity was assessed using modified neurological severity scores. Mitochondrial biogenesis and antioxidant response element expression were analyzed by RT-qPCR. Results: Our results demonstrated that intralesional administration of urocortin accelerated the resolution of hemorrhagic lesions, restored mitochondrial ATP levels, alleviated oxidative stress, and improved neurological outcomes in the Severe ICH allowing hematoma aspiration model. Urocortin treatment was associated with an increase in anti-inflammatory products while suppressing the production of pro-inflammatory cytokines and markers of oxidative stress during the acute phase of ICH. Conclusions: Intralesional administration of Urocortin exhibited neuroprotective effects in the Severe ICH-permitting hematoma aspiration rat model, highlighting its potential as a practical therapeutic strategy for severe ICH injuries.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

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Program #/Poster #: PSTR076.22/L7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant R01NS112350
NIH grant R01NS112308
NIH grant R01NS108756

Title: Transcriptional regulation across myeloid cells after status epilepticus

Authors: A. S. ROOPRA[1], N. H. VARVEL[2], ***R. DINGLEDINE**[2];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Emory Univ. Sch. Med., Atlanta, GA

Abstract: Analysis of a multi-center transcriptome study pointed to a prominent role for EZH2 in driving gene expression in dentate granule cells across multiple models of status epilepticus (SE) (Khan et al. Plos One, 2019). To confirm this finding and explore the regulation of gene expression across multiple hippocampal cell types, we combined the MAGIC algorithm (Roopra, PLOS Comp. Biol 2020) and single nucleus RNAseq to hippocampal tissue harvested 4 days after pilocarpine-induced SE. Data were obtained from 5 pilocarpine-treated and 4 saline-treated 8 week old C57BL/6NCrl male mice after the quality-control process. Altogether, full transcriptomes were obtained from 84,796 individual cells. Clusters of cells based on transcriptome similarity were visualized with Uniform Manifold Approximation and Projection (UMAP). Well-separated discrete cell clusters within UMAP projection space were obtained for dentate gyrus, pyramidal cell regions, astrocytes, myeloid cells and oligodendrocytes. Within each of these clusters only minimal overlap was seen between pilocarpine and saline-treated mice. We applied the MAGIC algorithm to identify the most prominent transcriptional drivers in the myeloid cluster after pilocarpine. Down-regulated genes in myeloid cells were driven primarily by transcriptional repressors REST, MIER1 and EZH2, but also by the histone methyltransferase EHMT2 (aka G9a) and SMARCA4, which functions in chromatin remodeling. Interestingly, the two most prominent actors in up-regulated genes in activated microglia were IKZF1 and IKZF2, which encode Ikaros-family transcription factors that act widely throughout the immune system. The myeloid cluster was disambiguated into 11 subclusters, most of which could be identified from their transcriptome profile as freshly infiltrated monocytes (2 clusters), naïve (resting) microglia, perivascular macrophages, and activated microglia (5 clusters). The activated microglia were loosely classified as M1 (2 subclusters, pro-inflammatory) and M2 (3 anti-inflammatory subclusters, two of which had characteristics of Disease-Associated Microglia). Studies are underway to compare transcriptional drivers in the activated microglia subclusters. Overall, these results demonstrate the creation of multiple distinct subclasses of activated microglia after status epilepticus.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

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Program #/Poster #: PSTR076.23/L8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 2664045

Title: Multisensory gamma entrainment as a pro-remyelination and anti-neuroinflammatory therapeutic strategy in demyelinating diseases

Authors: *D. RODRIGUES AMORIM[1], L. BOZZELLI[1], T. KIM[1], M. ISLAM[1], L. LIU[1], M. MURDOCK[1], F. GALIANA-MELENDEZ[1], F. ABDURROB[1], L.-H. TSAI[2];

[1]Picower Inst. for Learning and Memory, [2]Picower Inst. for Learning and Memory, Dept. of Brain and Cognitive Sciences, Broad Insti, MIT, Cambridge, MA

Abstract: Demyelination refers to the loss of the protective myelin sheath surrounding nerve fibers and supporting cells in the nervous system [1]. As a consequence, axons become highly vulnerable to insults, suffering profound atrophy and neuro-axonal degeneration[2]. Demyelination is a common pathological feature observed in various central nervous system (CNS) disorders. Several pathomolecular processes contribute to brain damage, including neuroinflammation, oligodendrocyte (OLs) cell death, demyelination and progressive neuronal dysfunction [3]. Previously published studies have established that the non-invasive gamma entrainment using sensory stimulation (GENUS) at 40Hz can preserve neuronal and synaptic density, induce changes in glial cell response, and prevent brain atrophy in Alzheimer's disease (AD) [4-6]. In this study, we utilized the cuprizone (CPZ) model to investigate the effectiveness of GENUS in promoting myelination and reducing neuroinflammation. Our findings demonstrate that GENUS significantly mitigated demyelination, stimulated the generation of new OLs in the corpus callosum (CC), and preserved synaptic plasticity, even during the peak cytotoxicity caused by CPZ. Furthermore, GENUS effectively attenuated ferroptosis-induced cell death in OLs. Additionally, chronic application of GENUS led to a substantial reduction in brain inflammation, decreasing microgliosis, astrogliosis, and levels of proinflammatory molecules, such as complement component 1q (C1q) and high mobility group box 1 (HMGB1). Given its ability to promote remyelination and suppress neuroinflammation, chronic GENUS therapy holds promise as a potential treatment for demyelinating disorders.
1. Stadelmann, C., Timmler, S., Barrantes-Freer, A. & Simons, M. Myelin in the central nervous system: Structure, function, and pathology. *Physiol. Rev.* **99**, 1381-1431 (2019).2. Love, S. Demyelinating diseases. *J. Clin. Pathol.* **59**, 1151-1159 (2006).3. Molina-Gonzalez, I., Miron, V. E. & Antel, J. P. Chronic oligodendrocyte injury in central nervous system pathologies. *Commun. Biol.* **5**, 1-11 (2022).4. Martorell, A. J. *et al.* Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. *Cell* **177**, 256-271.e22 (2019).5. Adaikkan, C. *et al.* Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. *Neuron* **102**, 929-943.e8 (2019).6. Chan, D. *et al.* Gamma frequency sensory stimulation prevents brain atrophy, improves sleep and memory in probable mild Alzheimer's patients. *Alzheimer's Dement.* **17**, e054218 (2021).

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

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Program #/Poster #: PSTR076.24/M1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 AG050518
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Dpt of Veteran's Affairs Grants IO1BX001804

Title: Orexin/hypocretin modulation of neuroinflammation: implications for age-related cognitive decline

Authors: *M. A. FRICK[1], B. SOMERA[4], J. L. WOODRUFF[2], L. P. REAGAN[5], J. R. FADEL[3]; [2]WJB Dorn VA Med. Ctr., [3]Univ. of South Carolina Sch. of Med., [1]Univ. of South Carolina, Columbia, SC; [4]Med. Col. of Georgia at Augusta Univ., Augusta, GA; [5]Univ. of South Carolina Sch. of Med., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: The orexin/hypocretin neuropeptide system, primarily found in the lateral hypothalamus and perifornical region, projects to multiple brain regions, and modulates sleep, wakefulness, appetite, and cognitive functioning. One region with dense orexinergic projections is the basal forebrain, which is the major source of acetylcholine in the neocortex and limbic structures such as the hippocampus and amygdala. The basal forebrain cholinergic system mediates cognitive functions and has been implicated in many neurodegenerative diseases, including Alzheimer's disease. We have previously shown that aging reduces orexin signaling and leads to dysfunctional cholinergic neurotransmission, but the mechanisms responsible for such deficits remain poorly understood. It has been suggested that orexin may be neuroprotective, and the age-related loss of orexin neurons diminishes the brain's anti-inflammatory response. Here, we investigate how the loss of orexin neurons exacerbates neuroinflammation in the basal forebrain. Orexin expression was knocked down using lentivirus mediated expression of preproorexin antisense administered into the lateral hypothalamus of young adult (3 months), male and female Fisher 344/Brown Norway F1 hybrid rats. Ten days later, a neuroinflammatory response was induced with a lipopolysaccharide (1 mg, intraperitoneal) challenge and microglial activation was assessed by quantitative and morphological examination, and cytokine analysis. Preliminary findings indicate that knockdown of orexin expression increases total microglia in the basal forebrain and levels of the pro-inflammatory cytokines IL-6 and TNF-α, indicating a dysfunctional inflammatory response. Loss of orexin expression in aging may facilitate neuroinflammatory processes that contribute to neurodegeneration and cognitive decline.

Disclosures: M.A. Frick: None. **B. Somera:** None. **J.L. Woodruff:** None. **L.P. Reagan:** None. **J.R. Fadel:** None.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.25/M2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Evaluation of human induced pluripotent stem cell (hiPSC)-derived tri-culture as in vitro model for neuroinflammation

Authors: *I. ONOFRE, C. FORMICA, L. SMIT, J. DCOSTA, S. JAIN;
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Abstract: The development of physiologically relevant models for neuroinflammation remains a challenge with an unfilled gap in translatable human-based platforms. Ncardia developed human tri-culture models composed of neurons, astrocytes and microglia derived from iPSCs, resembling physiological conditions that allow modulation of neuroinflammation and neurodegeneration *in vitro*. We characterized the tri-culture model for cell type ratio (MAP2/GFAP/IBA1), synaptic density (synaptophysin/PSD-95) and microglia activation for major biological processes that occur in the human brain: release of pro-inflammatory cytokines (IL-6, TNF-α, IL1-β and IL-18), phagocytic activity and morphological alterations. We observed tri-cultures exposed to lipopolysaccharide (LPS) released higher levels of IL-6, TNF-α, IL1-β and IL-18, exhibited higher phagocytic activity assessed by uptake of pHrodo Bioparticles and changed morphology to ameboid shape. In a next step, we established a tauopathy model in the tri-culture, by inducing the phosphorylation (pTAU) and aggregation of TAU, using recombinant mutant Tau (pre-formed fibrils) PFFs. This approach enabled a multi-parametric readout of neuronal and glial phenotypes including synaptic pruning and activation of microglia and astrocytes in the tri-culture. Upon the addition of TAU PFFs, microglial pruning, evident by the decrease in the synaptic markers synaptophysin and PSD-95 in neurite structures and detection of engulfed PSD-95 within the microglia. We observed increased levels of phagocyted pTAU by microglia, mostly dependent on the phagocytosis of neurons expressing pTAU and also increased levels of release of IL-6, TNF-α, IL1-β and IL-18. Together, these observations support a neurodegenerative phenotype, typical of tauopathies in which secreted or engulfed pTAU activates microglia initiating the neuroinflammatory cascade. The development and validation of models of relevant biological disease processes, such as microglia-neuron communication provides insight on cellular interactions that play a role in recognizing apoptotic neurons and modulating neuronal activity which are crucial events in disease progression. Targeting these pathways in human models with a combination of readouts allows interrogation and evaluation of the ability of therapeutics on rescuing primary, secondary and tertiary neuro-pathological signatures.

Disclosures: **I. Onofre:** A. Employment/Salary (full or part-time):; Ncardia. **C. Formica:** A. Employment/Salary (full or part-time):; Ncardia. **L. Smit:** A. Employment/Salary (full or part-time):; Ncardia. **J. DCosta:** A. Employment/Salary (full or part-time):; Ncardia. **S. Jain:** A. Employment/Salary (full or part-time):; Ncardia.

Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.26/M3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Dysregulation of histone deacetylase 6 in diabetic retinopathy

Authors: *J. KIM, J. JUN, D.-G. JO;
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Abstract: Diabetic retinopathy is a leading cause of vision loss in developed countries, characterized by the growth of abnormal blood vessels in the retina. It typically develops 10 to 15 years after the diagnosis of diabetes and is strongly influenced by disease duration and uncontrolled blood glucose levels. Recent studies have highlighted the effectiveness of anti-VEGF antibodies in diabetic retinopathy treatment. However, the optimal frequency and duration of treatment remain unclear. Histone deacetylase(HDAC) 6 is a Class IIb HDAC enzyme that plays a crucial role in various cellular processes, including gene expression, protein stability, localization, and functions, by removing acetyl groups from lysine residues of histone and nonhistone proteins. HDAC6 inhibitors have been extensively studied in the context of cancer, inflammatory diseases, and neurodegenerative disorders. In this study, we evaluated the role of HDAC6 in the pathogenesis of diabetic retinopathy. Our findings confirmed the increased activity of HDAC6 in diabetic retinopathy, which was associated with inflammation, hemorrhage, neurodegeneration, and a decrease in blood-retinal barrier integrity. Additionally, we observed improved pathological outcomes in HDAC6 knockout models, further supporting the involvement of HDAC6 in the disease. Additionally, our group developed an orally available HDAC6-specific inhibitor, which also demonstrated efficacy in ameliorating diabetic retinopathy. In conclusion, our findings suggest that HDAC6 is implicated in the development of diabetic retinopathy, and both genetic knockout and pharmacological inhibition of HDAC6 show promise in improving the disease pathology. These findings highlight HDAC6 as a potential therapeutic target for the treatment of diabetic retinopathy.

Disclosures: **J. Kim:** None. **J. Jun:** None. **D. Jo:** None.

Poster

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.27/M4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NS103212
NS122174

Title: Dissecting the role of H-2Db class I molecule in the development of brain atrophy during Theiler's murine encephalomyelitis virus (TMEV) infection

Authors: *K. WININGER[1], E. GODDERY[2], K. AYASOUFI[3], D. WOLF[2], Z. P. TRITZ[3], F. JIN[2], M. J. HANSEN[2], A. J. JOHNSON[3];

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Abstract: Brain atrophy is a common feature of many neurological diseases as diverse as Alzheimer's disease, cerebral palsy, Huntington's disease, multiple sclerosis, epilepsy, encephalitis, neurosyphilis, neuroAIDS, and Covid-19 infection. We have developed a murine model of brain atrophy using the Theiler's murine encephalomyelitis virus (TMEV) infection mouse model of multiple sclerosis. In this study, we investigated the contribution of the MHC class I molecule, H-2D^b, in generating an immune response associated with the onset of brain atrophy using mice with a C57BL/6 background. The H-2D^b Class I molecule not only contributed to significantly more ventricular enlargement in a T2-weighted MRI at 28 dpi., but this ventricular enlargement correlated to CD8 T cell and myeloid cell infiltration. To further define the cellular and molecular mechanisms of MHC class I molecules in TMEV induced brain atrophy we investigated the cell specific contribution of brain resident antigen presenting cells (APCs) in ventricular atrophy. We developed novel bi-transgenic mouse lines with tamoxifen induced conditional ablation of the H-2D^b class I molecule in Cx3CR1+ brain resident myeloid cells. Cx3CR1cre+/D^b Lox P mice presented with significantly less ventricular atrophy at 45 dpi., compared to cre- littermates. Likewise, Cx3CR1+/D^b Lox P mice exhibited a decrease in CD8 T cell and myeloid cell infiltration as compared to cre- littermates. These results strongly imply that antigen presentation by H-2D^b on CNS resident myeloid cells, at least in part is responsible for the development of ventricular atrophy, and TMEV induced ventricular atrophy may be a result of immune cell infiltration.

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Poster

PSTR076. Neuroinflammation: Beyond Microglia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.28/M5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant Award DA046258

Title: Telmisartan Attenuates COVID-19-induced Neurological Abnormalities in PC-12 Cells

Authors: J. ZHANG[1,2], M. BISHIR[1,2], R. PATEL[1,2], *S. CHANG[2,1];
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Abstract: Infection of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) leads to the development of Coronavirus Disease-19 (COVID-19). Receptor-mediated endocytosis of the virus via angiotensin-converting enzyme-2 (ACE2) initiates systemic inflammation. Our initial network meta-analysis investigations using Ingenuity Pathway Analysis (IPA), a bioinformatics tool, demonstrated that COVID-19 contributes to the activation of the neuroinflammation

signaling pathway (NISP), which is linked to neurodegenerative disorders such as Parkinson's disease (PD). In our study, we integrate in-silico, in-vivo, and in-vitro studies to suggest telmisartan as a potential therapeutic strategy for COVID-19 augmentation of neurodegenerative disorders. First, we have used in-silico tools to analyze differentially expressed genes from postmortem brain samples of COVID-19 patients (GSE159812) to reveal enriched pathways and biological functions. Next, we have used IPA to identify drugs to mimic COVID-19 inflammation using 1) lipopolysaccharide (LPS) to model generalized inflammation and 2) cytokine cocktail to model cytokine storm in COVID-19. We identified telmisartan, an antihypertensive drug, as a potential neuroprotective therapeutic drug with a two-pronged role in counterbalancing COVID-19's modulation of the NISP and ACE2 expression. Then, we used differentiated PC-12 cells treated with 1-methyl-4-phenylpyridinium (MPP+) and 6-hydroxydopamine (6-OHDA) to induce PD-like symptoms followed by LPS and cytokine cocktail treatment to mimic COVID-19 inflammation. Finally, by performing MTT viability assay, cytokine ELISA, ACE2 RT-qPCR, and RNA-seq analysis were to measure neurotoxicity and disruption of the renin-angiotensin pathway. We found that 6-OHDA and cytokine cocktail increased neuronal cell death. Treatment with telmisartan reversed COVID-19 cytokine storm-induced neurological abnormalities. Taken together, telmisartan treatment was found to be a promising therapeutic approach for attenuating COVID-19-induced augmentation of neurodegeneration.

Disclosures: J. Zhang: None. **M. Bishir:** None. **R. Patel:** None. **S. Chang:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.01/M7

Topic: C.08. Ischemia

Support: NIH Grant F31NS124280 (GF)
NIH Grant F99AG079793 (GF)
NIH Grant R01NS120322 (TH)

Title: Characterization of the intramitochondrial proteostatic response in a primary neuron model of ischemia/reperfusion injury

Authors: *G. M. FOGO[1], S. RAGHUNAYAKULA[2], F. TORRES TORRES[1], K. J. EMAUS[1], J. M. WIDER[2], T. H. SANDERSON[1,2,3];
[1]Neurosci. Grad. Program, [2]Emergency Med., [3]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Cerebral ischemia/reperfusion (I/R) injury (e.g. stroke) continues to be a leading cause of disability and death. Mitochondrial dysfunction is a prominent component of I/R injury and a key driver of secondary brain injury. Function of the mitochondrial network is tightly connected

to its form and proteostatic makeup. The quality control (QC) mechanisms of mitophagy and intramitochondrial proteostasis critically act to ensure efficient and sufficient energy production. Although the temporal patterns of mitophagy have been described in neuronal I/R injury, the proteostatic response is less well understood. Mitochondria are home to a number of unique proteases that maintain homeostasis through the processing/turnover of the mitochondrial proteome. To assess the level of mitochondrial protein turnover in response to I/R, we expressed the MitoTimer reporter in mouse primary cortical neurons following oxygen/glucose deprivation (OGD). Ratiometric measurements of old/oxidized (red) and newly synthesized (green) MitoTimer protein were taken to assess protein turnover. We observed a marked increase in oxidized MitoTimer protein turnover at 2 hours of reperfusion following OGD. Protein turnover did not remain elevated and decreased with time during reperfusion. This effect is not exclusively the result of mitophagy, as mitochondrial protease activity was increased at 2 hours reperfusion, as assessed by in vitro FITC-casein assay with isolated mitochondria. However, blanket increases in mitochondrial protease activity were not observed. Proteolytic processing of Opa1, typically driven by the mitochondrial proteases Oma1 and Yme1L, was increased during OGD, but not exacerbated by reperfusion, suggesting specificity of the proteolytic upregulation. Because MitoTimer assays the degradation of an oxidized protein, we suspected the intramitochondrial protease LonP1 to be a potential causative agent. Intriguingly, LonP1 protein expression and levels of known LonP1 degradative targets were not significantly altered after injury. To probe the interactions between QC and dynamics pathways, we assessed protein turnover and protease activity in Parkin, Drp1, and Opa1 KO neurons. Alterations in these mechanisms rewire mitochondrial proteostasis at baseline conditions and after OGD, demonstrating that mitochondrial dynamics and QC pathways work in coordination to ensure homeostasis and respond to injury. Current efforts are focused on identifying the specific protease(s) involved in the proteolytic peak observed during reperfusion and how remodeling of the mitochondrial proteome impacts death and dysfunction observed in neuronal I/R injury.

Disclosures: **G.M. Fogo:** None. **S. Raghunayakula:** None. **F. Torres Torres:** None. **K.J. Emaus:** None. **J.M. Wider:** None. **T.H. Sanderson:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.02/M8

Topic: C.08. Ischemia

Support: NIH NS124722 NS102495 (XZ)
AHA 23CDA1051498 (WS)

Title: Acidosis disrupts brain microvascular endothelial cell junctional integrity in vitro

Authors: W. SUN[1], *X. ZHA[2];
[1]Pharmacol. and Pharmaceut. Sci., [2]Univ. of Missouri Kansas City, Kansas City, MO

Abstract: Acidosis occurs in a wide range of neurological diseases including brain ischemia. Acidosis-induced neurotoxicity has been extensively investigated. In contrast, there are relatively fewer studies on how acidosis regulates brain microvascular endothelial cells (BMEC), which are important for blood-brain barrier functionality. A better understanding of acid signaling in BMEC junctional integrity has important implications for therapeutic interventions of multiple neurological diseases. Here, we examined the effect of acidosis on BEND3 cells, a mouse BMEC cell line. To investigate acidosis-induced signaling, we treated BEND3 cells with pH 7.4, 6.4, and 6.0 for up to 6 hours, and analyzed with Western blot for the activation of downstream signaling. Acidosis induced PKA-dependent signaling in a time-dependent manner. Prolonged acidosis also reduced the expression of cell junctional markers. We then performed immunostaining to visualize the changes in cell junctional proteins. Acidosis reduced the junctional localization of ZO-1 and occludin. To determine whether these changes correlated with BEND3 junctional permeability, we used the in vitro transwell culture. After one week in culture, BEND3 cells form tight connections. We then treated the transwells with different pH for up to 6 hours and measured TEER at 2 and 6 hr. Acidosis induced a time-dependent reduction in TEER. These data suggest that acid-induced signaling correlates with junctional disruption and increased permeability in BMEC.

Disclosures: W. Sun: None. **X. Zha:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.03/Web Only

Topic: C.08. Ischemia

Support: CONACYT 156906

Title: Focal cerebral ischemia and reperfusion injury causes changes in mitochondrial protein expression at early times. Study in a rat model

Authors: *A. ORTIZ-PLATA[1], R. A. GÓMEZ RIVERA[2], N. SERRANO[3], M. OROZCO-IBARRA[4], L. CORTÉS MARTÍNEZ[5], F. CÁZARES RAGA[7], J. NADER KAWACHI[8], F. HERNÁNDEZ HERNÁNDEZ[6];
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Abstract: ABSTRACT: The brain to maintain its functional integrity requires a lot of energy that is obtained in the mitochondria through aerobic glycolysis and oxygen reduction. During focal cerebral ischemia (FCI) oxygen and glucose supply decrease, ATP production is impaired, and gene and protein expression change. In our work group, expression changes of genes and cytosol proteins have been found, at short times of focal cerebral ischemia. Here mitochondrial protein expression changes were analyzed. FCI (occlusion of middle cerebral artery) in male Wistar rats was induced for 15 minutes and one hour without and with 24 hours of blood reperfusion (rpf); proteomic maps of the striatal and hippocampal brain regions were prepared, differential protein spots were selected, and identified by mass spectrometry. Thirteen protein spots with differential expression among the experimental groups were selected. Expression spot density was assessed with ImageJ 1.49V program (Wayne Rasband, National Institutes of Health, USA. http://imageJ.nih.gov/IJ), and ANOVA statistical analysis was done (T test; $p<0.05$). It was identified proteins involved in glycolysis and ATP synthesis, which significantly decreased ($p<0.05$) the expression in hippocampus at 15 min of FCI with and without reperfusion. In the striatum, they did not show significant changes; One spot was identified as Calmodulin, which increased in the hippocampus at 1 h-FCI (<0.05) and decreased in the striatum at 15 min and 1h/24 rpf but not significantly; α-syn increased in hippocampus at 15 min, 15min/rpf and 1h/rpf (<0.05), in striatum increase in rpf in both times; β-syn increase in striatum in rpf conditions (<0.05) in hippocampus increased but without significance; mitocondrial elongation factor Tu decrease in hippocampus and increase in striatum; Prohibitin decrease in hippocampus at 15 min FCI and gradually increases in rpf , 1h and 1h/rpf. The analysis of the expression of mitochondrial proteins in FCI showed that mitochondria is susceptible to ischemic damage from the first minutes of ischemia, altering not only the vital function of energy generation and the proteins involved in calcium homeostasis, response to the REDOX state, and regulation of neurotransmitters, but also those involved in protein synthesis, in addition to those of response to ischemic damage involved in neuronal plasticity, stabilization of the mitochondrial genome, its morphology, and apoptosis. The evaluation of protein showed that the response to damage is different in the two brain regions. Protein characterization will contribute to broaden the knowledge of the events that occur in response to FCI opening therapeutic possibilities.

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Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.04/M9

Topic: C.08. Ischemia

Support: NRF of Korea Grant 2021R1A2C2010920)

Title: Modulation of systemic iron level by HMGB1 after cerebral ischemia via stimulating hepcidin induction in hepatocytes

Authors: *J.-K. LEE[1], D. DASHDULAM[2], S.-A. OH[1], S.-I. SEOL[1];
[1]Inha Univ. Sch. of Med., Inchon, Korea, Republic of; [2]Anat., Inha Univ. Sch. of Med., Incheon, Korea, Republic of

Abstract: Dysregulation of cellular iron homeostasis contributes to neural damage in ischemic brain and elevated iron levels have also been observed in patients with stroke. In a previous report, we showed that High mobility group box 1 (HMGB1), a pro-inflammatory prototypic danger-associated molecular pattern, serves as a ferroptosis inducer in the post-ischemic brain by upregulating hepcidin in astrocytes, thereby aggravating acute damage. Since hepatocyte is a main cell type to produce hepcidin, playing a key role in systemic iron modulation, in the present study, we investigated hepcidin induction in liver after cerebral ischemia and examined a role played by HMGB1. We found upregulation of hepcidin expression occurred in liver as early as 3 h post-MCAO and it was rapidly increased until 24 h and then gradually decreased. Immunohistochemisry revealed that hepcidin was mainly detected in hepatocytes. In addition, we detected FPN, the only iron exporter downregulated by hepcidin, was decreased and intracellular iron, DMT1, ferritin heavy chain, and ferritin light chain were all upregulated in liver parenchyma 12 h post-MCAO. HMGB1 was significantly induced in liver and importantly, dsHMGB1 was the main subtype accumulated in liver tissue after MCAO. It is interesting to note that a marked induction and nuclear to cytoplasmic translocation of HMGB1were detected in hepatocyte, although similar observations were also made in Kupffer cells. Moreover, we demonstrate that treatment with recombinant disulfide-HMGB1 stimulated AML12 cell, a hepatocyte cell line, to induce hepcidin expression in a TLR4-dependent manner and STAT3 and JNK signaling pathways were also involved in dsHMGB-mediated hepcidin upregulation in hepatocytes. These findings show that dsHMGB1 mediates hepcidin induction in hepatocytes, contributing to systemic iron surge after cerebral ischemic insult.

Disclosures: **J. Lee:** None. **D. Dashdulam:** None. **S. Oh:** None. **S. Seol:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.05/M10

Topic: C.08. Ischemia

Support: CalciGenix, LLC

Title: Differential effect of oxygen-glucose deprivation on signal-to-noise ratio in male and female CA1 neurons

Authors: *I. MORLEY[1], B. NATWORA[1], M. MASSMAN[1], J. R. MOYER, Jr.[1,2];
[1]Psychology, [2]Biol. Sci., Univ. of wisconsin Milwaukee, Milwaukee, WI

Abstract: Stroke is the fifth leading cause of death in the United States, often resulting in cognitive deficits for those who survive. Medial temporal lobe structures, such as the hippocampus, play an important role in cognitive functions, particularly learning and memory. As a result, understanding how ischemia impacts hippocampal neurons is essential to developing treatments to preserve their functionality following a stroke, which may help preserve cognitive functions. The present study exposed acute brain slices to oxygen-glucose deprivation (OGD) as a model of ischemic stroke in combination with visually-guided whole-cell recordings to study the impact of OGD on CA1 neurophysiological properties. Signal-to-noise ratio (SNR), defined as the variance of the signal divided by the variance of the noise, is one effective measure of overall efficiency and fidelity within neural systems. Thus, in addition to standard neurophysiological measures, the present study focused on SNR as an assessment of membrane alterations induced from an ischemic insult. Coronal brain slices that included the hippocampus were prepared from male and female F344 rats and placed in oxygenated-aCSF. Half the slices underwent 5 minutes of oxygen-glucose-deprivation (OGD), while the other half remained in oxygenated-aCSF. To confirm the effectiveness of the OGD, a subset of the slices acquired from each animal were assayed using the Trypan blue exclusion method. To assess the impact of OGD on membrane properties within the cell, WCRs were obtained from the remaining hippocampal CA1 slices. CA1 neurons from male and female rats in the OGD condition exhibited significant cell death as measured by a significant increase in the number of Trypan blue labeled neurons. SNR significantly increased in the male, but not female CA1 following OGD. Thus, preliminary data suggest that OGD may differentially increase intrinsic excitability in male but not female rat CA1 neurons. Further evidence of an increase in intrinsic excitability following OGD was found as a significantly decreased membrane time constant (tau) following depolarizing current injections. In conclusion, ischemia may differentially increase neuronal signal-to-noise ratio as well as increase certain measures of intrinsic excitability in CA1 from male but not female rats. These observed alterations may help define certain sex-specific changes in CA1 following an ischemic insult and shed light on potential neurotherapeutic targets as well as provide an intriguing basis for future research on intrinsic excitability following ischemia.

Disclosures: I. Morley: None. **B. Natwora:** None. **M. Massman:** None. **J.R. Moyer:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.06/N1

Topic: C.08. Ischemia

Title: Features of structural degeneration and recovery of the rat hippocampus after occlusion and ligation of the common carotid arteries

Authors: *V. AKULININ, L. MAKARYEVA, S. STEPANOV, A. SHORONOVA, D. AVDEEV, M. KORZHUK;
Omsk State Med. Univ., Omsk, Russian Federation

Abstract: The features degeneration and recovery of the nervous tissue of the hippocampus of white rats after occlusion of the common carotid arteries (OCCA, group 1) and ligation of the common carotid arteries (LCCA, group 2) were studied. The experiment was carried out on Wistar rats. We used unilateral and bilateral, OCCA and LCCA. Intact animals (n=6) served as controls. The brain was collected 1, 3, 7, 14, and 30 days after exposure. Frontal sections of the hippocampus were stained with Nissl, hematoxylin-eosin, immunohistochemical typing was performed NSE, GFAP, IBA1, MAP2, p38. The numerical density of neurons, astrocytes, microgliocytes, oligodendrocytes, the content of normo-, hypo-, hyperchromic neurons, the relative area of edema/swelling zones and terminals in the neuropil were determined (various ImageJ 1.53 plugins). Statistical analysis was performed using nonparametric methods. After a short-term OCCA, there were clear signs of diffuse-focal de- and hyperhydration, as well as the reaction of neuroglial cells. Hypochromic neurons with signs of homogenization, pronounced manifestations of edema-swelling, pycnomorphic neurons. In group 2, neurons with signs of irreversible damage persisted even after 30 days. During 1-3 days, in groups 1 and 2, the predominance of degeneratively altered neurons was noted, many dark neurons were noted during 7-14 days against the background of high preservation of the systems of interneuronal communication and the cytoskeleton of neighboring neurons. It was found that 1 day after OCCA and LCCA, the peaks of the neuropil image were redistributed according to the integral indicator - the total pixel intensity. Thus, after prolonged occlusion (40 min) and LCCA without subsequent reperfusion, the system of natural protection and restoration of ischemically altered neurons of the fields CA_1 and CA_3 of the hippocampus is irreversibly damaged - the microdrainage function of astrocytes. Degeneration of the cytoskeleton of astrocytic processes, their prolonged edema around neurons and death of neurons through the mechanisms of secondary ischemia - capillary compression, energy deficiency, disruption of the glutamate-glutamine cycle and ion homeostasis, activation of necrosis and apoptosis. Therefore, we believe that manifestations of de- and hyperhydration of the hippocampus after OCCA, not accompanied by the destruction of astrocyte processes, can be considered as predominantly reversible protective within the framework of reactive astrogliosis, and in the long-term period after ligation of the common carotid artery - as a sign of intravital degenerative changes in neurons. and astrocytes.

Disclosures: V. Akulinin: None. **L. Makaryeva:** None. **S. Stepanov:** None. **A. Shoronova:** None. **D. Avdeev:** None. **M. Korzhuk:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

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Topic: C.08. Ischemia

Support: National Institute of Neurological Disorders and Stroke, R01NS131484
LSU Health Shreveport – Center for Applied Immunology and Pathological Processes, P20GM134974

Title: Brain-derived neurotrophic factor signaling through tropomyosin related kinase B receptors promotes neural regeneration and functional recovery following pediatric stroke

Authors: *N. AICH[1], R. MARQUEZ-ORTIZ[1], B. AKHTER[1], M. BRADFORD[1], K. RODGERS[2];
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Abstract: Introduction: Replacement of neurons lost following ischemia, either via enhanced endogenous neurogenesis or stem cell therapy, has been highly sought, but low survival rate of newly generated neurons in adults has left doubt about the therapeutic potential of adult neurogenesis. However, stroke in the young injured brain reveals a greater degree of plasticity and capacity for repair compared to adults. Using a pediatric model of stroke, we discovered a remarkable neural regenerative response in pediatric compared to adult mice at 30d, along with improved post-ischemic recovery. Our findings suggest a possible mechanism is brain-derived neurotrophic factor (BDNF) signaling through its tropomyosin related kinase B (*TrkB*) receptor, as we observed marked increases in BDNF expression and phosphorylated TrkB in the injured pediatric striatum compared to adult. Further, BDNF was primarily released by neurons in pediatric and astrocytes in adult mice, which may explain age-related differences in regeneration and recovery since recent reports suggest astrocytic BDNF is pathological and modulates neuronal dysfunction. BDNF is known to support neural survival, outgrowth of axons and dendrites, synaptogenesis/remodeling, and synaptic transmission. There has been much focus on adult BDNF-TrkB signaling in rodent models of cerebral ischemia, but there is little evidence of brain regeneration and recovery. However, we have found both in pediatric mice, and this is in spite of extensive neuronal cell death and similar infarct size in both age groups at acute time points (24hr). At 30d, we observe a robust regenerative neuronal response along with improved motor and *in vivo* electrophysiological recovery in MCAO-injured pediatric mice compared to adults. Our findings suggest BDNF-TrkB signaling has a powerful age-related influence on neural regeneration and post-ischemic functional recovery.**Methods:** BDNF-TrkB signaling was examined following experimental stroke (MCAO) using immunofluorescence, Western blots, ELISA, neurobehavioral measures, and *in vivo* electrophysiology.**Results:** Increased BDNF and pTrkB expression was found at acute, sub-acute, and chronic timepoints (72hr, 14d, and 30d) post-ischemia in MCAO-injured pediatric mice, and this was accompanied by improved neural regeneration and motor recovery/neuroplasticity compared to adult mice. **Conclusions:** BDNF-TrkB signaling is supportive following pediatric stroke and interventions enhancing BDNF expression (i.e., TrkB agonism) may offer alternative strategies for stroke treatment. Potentially promoting post-ischemic neural repair, synaptic plasticity, and functional recovery.

Disclosures: N. Aich: None. **R. Marquez-Ortiz:** None. **B. Akhter:** None. **M. Bradford:** None. **K. Rodgers:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.08/N3

Topic: C.08. Ischemia

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Title: Sur1-trpm4- and ncx1-mediated cation flux drives aqp4-dependent water flux at the astrocyte endfeet during post-ischemic brain swelling

Authors: *B. SHIM[1,2], J. A. STOKUM[3], S. NEGOITA[3], N. TSYMBALYUK[3], O. TSYMBALYUK[3], S. IVANOVA[3], K. KELEDJIAN[3], V. GERZANICH[1], J. M. SIMARD[3,4,5]; [1]Univ. of Maryland, Baltimore, Baltimore, MD; [2]Grad. Program in Mol. Med., [3]Neurosurg., [4]Pathology, [5]Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Brain swelling remains a robust indicator of clinical outcome in ischemic stroke and other acute CNS injuries. However, effective and target-specific therapies against brain swelling are currently lacking because the underlying molecular and cellular mechanisms remain unclear. Brain swelling is mediated by pathological ion channel activities that drive water accumulation through aquaporin-4 (AQP4), the most abundant brain water channel that are uniquely expressed at the perivascular astrocyte endfeet. Recent studies from cultured astrocytes demonstrated that hypotonicity- or hypoxia-induced surface translocation of AQP4 is a critical and potentially targetable mechanism in thwarting astrocyte swelling. Here, we aimed to elucidate a novel mechanism linking injury-specific ion channel activities to surface expression of AQP4 that may drive *in vivo* astrocyte and brain swelling in a mouse model of severe brain ischemia-reperfusion. To investigate post-ischemic brain swelling, we optimized the middle cerebral artery occlusion and reperfusion (MCAo/R) mouse model to decouple brain swelling from infarct size. In this MCAo/R model, the heteromeric cation channel SUR1-TRPM4 and the Na^+/Ca^{2+} exchanger NCX1 were upregulated in perivascular astrocyte endfeet. GCaMP calcium imaging of perivascular endfeet in post-ischemic brain slices increased Ca^{2+} influx upon opening the SUR1-TRPM4 channel that was inhibited using an NCX1 reverse-mode inhibitor. Slice biotinylation from post-ischemic brain tissues demonstrated an increase in surface expression, but not in total expression, of AQP4 in the ischemic hemisphere compared to its contralateral counterpart. The increased AQP4 surface translocation was reversed upon pharmacological inhibition *in vivo* of SUR1-TRPM4 or NCX1 as well as by cre-lox knockout of *Abcc8*/SUR1 and *Slc8a1*/NCX1 in astrocytes. Activation of SUR1-TRPM4 promoted astrocyte swelling, including at the somata and perivascular endfeet, in post-ischemic brain slices that was slowed by the NCX1 reverse-mode inhibitor. Finally, *in vivo* pharmacological inhibition of SUR1-TRPM4 or NCX1 as well as astrocyte-specific deletion of *Abcc8* and *Slc8a1* reduced hemispheric swelling without affecting infarct size, consistent with the established model of post-ischemic brain swelling.
The study overall highlights critical roles of the SUR1-TRPM4 ion channel and NCX1 exchanger that promote AQP4 surface localization, among other possible molecular mechanisms at the perivascular astrocyte endfeet, during post-ischemic astrocyte and brain swelling.

Disclosures: **B. Shim:** None. **J.A. Stokum:** None. **S. Negoita:** None. **N. Tsymbalyuk:** None. **O. Tsymbalyuk:** None. **S. Ivanova:** None. **K. Keledjian:** None. **V. Gerzanich:** None. **J.M. Simard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent, Remedy Pharmaceuticals, Biogen.

Poster

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Support: NINDS Grant K08NS114165-01A1
NRTS 2199

Title: Transcriptional response of Parvalbumin interneurons in the barrel cortex after photothrombotic stroke

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Abstract: Stroke is the fifth leading cause of death and a major cause of serious disability in the United States. Sensorimotor recovery is thought to be limited by GABAergic inhibition which curbs cortical excitability in the peri-infarct cortex. One type of interneuron, Parvalbumin (PV) interneurons (INs), provide direct peri-somatic inhibition to excitatory neurons and play an important role in circuit plasticity in normal, healthy cortex. However, the effects of stroke on PV cells and their specific role in regulating circuit excitability after stroke and sensorimotor recovery remains unclear. Some studies have shown reduction of PV gene expression in bulk RNA-sequencing during recovery from stroke, but single-cell PV RNA-sequencing in the context of stroke has not been done. Changes in molecular pathways of PV INs specifically may help explain their role at different phases after stroke. Here, we assessed transcriptional changes in PV cells at 1 and 4 weeks after a photothrombotic (PT) ischemic stroke in the mouse barrel cortex (S1BF) using a Ribotag approach. First, we generated PV-$Cre^{+/-}$;$Rpl22^{HA/-}$ double transgenic mice in which actively translating ribosomes in PV cells are tagged with the hemagglutinin (HA) epitope. We induced a PT stroke above the S1BF in 10-week-old mice. A second control group underwent sham PT strokes of the S1BF. At 1 or 4 weeks after the stroke, we dissected S1BF and used an anti-HA antibody to isolate ribosome-associated mRNA transcripts from PV INs. We are currently completing RNA-sequencing but expect we will find differentially expressed (DE) transcriptomes in injured vs non-injured states and that these changes may evolve over time. We are also performing gene ontology enrichment analysis to help elucidate how changes in the molecular pathways in PV cells can affect their function and role in the acute and subacute phases after stroke. We anticipate these results will help to define new molecular targets for promoting plasticity and functional recovery after stroke.

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Poster

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Topic: C.08. Ischemia

Support: NIH F31NS120422
NIH R01NS092645
NIH R01NS046072

Title: Persistent enhancement of postsynaptic GABA inhibition following global cerebral ischemia

Authors: *A. BURCH[1], J. D. GARCIA[2], H. O'LEARY[3], J. E. ORFILA[5], E. TIEMEIER[3], N. CHALMERS[4], N. QUILLINAN[3], K. R. SMITH[2], P. S. HERSON[5];
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Abstract: Cardiac arrest resulting in global cerebral ischemia (GCI) produces long-term cognitive impairment in a significant portion of survivors, yet the mechanisms underlying cognitive deficits are largely unknown. Using a mouse model of cardiac arrest/ cardiopulmonary resuscitation (CA/CPR), our lab has previously shown prolonged impairment in long-term potentiation (LTP) of hippocampal CA1 neurons, correlating with deficits in learning and memory tasks. Excitatory/ inhibitory (E/I) imbalance is involved in numerous neurologic disorders of cognition. We therefore hypothesized that E/I balance is disrupted in the post-acute phase following CA/CPR, leading to a reduction hippocampal LTP. To address this, we employed whole-cell patch-clamp electrophysiology and recorded from hippocampal CA1 neurons 7 days following CA/CPR. We measured the ratio of evoked inhibitory GABA responses to excitatory AMPA responses and found a significant reduction in the E/I ratio of evoked responses in CA/CPR mice (sham: 0.779± 0.052 vs. CA/CPR: 1.034± 0.085; p=0.042). To investigate whether increased inhibitory signaling might contribute to LTP impairment post-CA/CPR, we performed field electrophysiology experiments in the Schaffer collateral-CA1 region of the hippocampus and found bath application of a $GABA_A$ receptor inhibitor, picrotoxin, significantly restored LTP in CA/CPR brain slices (CA/CPR: 114.0%± 8.44, vs. CA/CPR+picro: 182.7%± 18.33; p=0.018). Next, we assessed whether the enhancement in inhibitory function was pre- or postsynaptic and recorded spontaneous inhibitory postsynaptic currents (sIPSC's) in CA1 neurons and found a significant increase in sIPSC amplitude following CA/CPR (sham: 50.55pA± 3.021, vs. CA/CPR: 70.75pA± 8.107 p=0.009), indicating enhanced postsynaptic GABA function. Interestingly, pharmacologic inhibition of the TRPM2 ion channel by tatM2NX

restored the CA/CPR effect on sIPSC amplitude CA/CPR+tatM2NX: 45.608pA± 2.207, vs. CA/CPR; p=0.002). Using an *in vitro* model of GCI, we find that hippocampal neurons subjected to oxygen-glucose deprivation (OGD) show a persistent increase in cluster area of $GABA_A$ receptors (25%, $p<0.0001$) and gephyrin (22%, $p<0.001$), the postsynaptic inhibitory scaffold protein. The increase in receptor density (37%, $p<0.001$) is reversed by blocking the TRPM2 channel at chronic timepoints following OGD. Taken together, these data support increased postsynaptic inhibitory function as a contributor to LTP deficits in the post-acute phase following GCI and identify the TRPM2 ion channel as a targetable mediator of this process.

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Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

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Topic: C.08. Ischemia

Support: NIH Grant NS121227

Title: Mechanisms of ROS generation after ischemia in CA1 neurons in acute brain slices

Authors: Y. V. MEDVEDEVA[1], E. WANG[1], ***J. WEISS**[2];
[1]Neurol., Univ. of California, Irvine, Irvine, CA; [2]Neurol., Univ. of California Irvine, Irvine, CA

Abstract: Despite high morbidity and mortality after brain ischemia, treatments are limited in part due to incomplete understanding of injury mechanisms. After transient ischemia many neurons initially recover but later die. Our recent studies using a mouse hippocampal slice oxygen glucose deprivation (OGD)/reperfusion model found that Zn^{2+} accumulation in CA1 neuronal mitochondria after ischemia (largely via the mitochondrial Ca^{2+} uniporter, MCU) contributes to delayed mitochondria dysfunction and neuronal damage. It has been long considered that reactive oxygen species (ROS) overproduction accelerates the delayed injury. To investigate the role of mitochondrial Zn^{2+} accumulation in post-ischemic ROS production and evaluate possible contributions of other factors we used our acute hippocampal slice OGD/reperfusion model. Slices were loaded with the ROS indicator dihydroethidium and subjected to short (6 min) episodes of OGD. We found that OGD evoked a considerable increase in ROS production in 3 phases: 1- an abrupt ROS acceleration 4-6 min after the start of OGD; 2- a marked slowing of ROS production to near basal levels after ~10 min; and 3- a 2nd sharp acceleration of ROS production starting 20-40 min after reperfusion. This second acceleration was almost completely blocked by Zn^{2+} chelation (with TPEN) applied after the withdrawal of OGD. Inhibition of the MCU (by RU265) administered after the end of OGD, prevented this secondary steep ROS acceleration, but resulted in a steady slow increase in ROS production

starting after the 1st phase and lasting up to 1h after OGD. These data suggest that while the late acceleration of ROS production is largely mediated by mitochondrial Zn^{2+} accumulation through the MCU, MCU blockade, and, thus prevention of mitochondrial Ca^{2+} buffering may hasten ROS production via activation of a cytosolic source. Indeed administration of the NADPH oxidase inhibitor apocynin along with RU265 blocked this slow ROS generation. Finally, we tested the effect of targeting mitochondrial hyperpolarization after reperfusion. Administration of FTY720 which we found causes a partial (5-10%) mitochondrial depolarization, prevented the late ROS acceleration, suggesting that mitochondrial hyperpolarization contributes to delayed ROS overproduction. Thus, mitochondrial Zn^{2+} accumulation, cytosolic Ca^{2+} accumulation, and reperfusion-induced mitochondria hyperpolarization all appear to contribute to ROS overproduction after ischemia. While cytosolic Ca^{2+} accumulation during ischemia may be hard to target, mitochondrial Zn^{2+} accumulation and hyperpolarization both occur after reperfusion and thus may be amenable to intervention.

Disclosures: **Y.V. Medvedeva:** None. **E. Wang:** None. **J. Weiss:** None.

Poster

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Topic: C.08. Ischemia

Support: Ontario Graduate Scholarship
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Title: Comparing hippocampal brain slicing temperatures: effects on slice health in rodent stroke models

Authors: *S. R. WOLKOFF, P. J. GAGOLEWICZ, R. D. ANDREW;
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Abstract: Following an ischemic stroke, recurrent spreading depolarization (SD) across the grey matter of the brain is the primary contributor to acute neuronal injury. Within only minutes of the brain being deprived of oxygen and glucose, production of adenosine triphosphate (ATP) is rapidly terminated, causing the ATP driven Na+/K+ pumps on neuronal membranes to fail and membrane potential to be lost. As a result, a wave of SD propagates through higher grey matter of the brain, injuring neurons in its wake. While SD originates near the ischemic core, recurrent SDs spread across and expand the penumbra over hours. Accordingly, this represents a potential therapeutic window where inhibition of penumbral SDs prevent neuronal injury and to improve stroke patient outcome. SD can be induced in rodent brain slices to study the underlying molecular mechanisms. Brain slicing is a fundamental method used in cellular neuroscience research, and it is common practice to submerge the brain in near-zero degrees Celsius artificial

cerebrospinal fluid (aCSF) throughout the dissection and slicing process. It is believed that slicing in cold temperatures helps preserve the brain and facilitate firmer slicing; however, we have seen evidence in the Andrew lab that brains cooled to ~5°C will undergo a bout of 'cold SD.' This led us to question whether brain slices prepared in warmer conditions may be of better quality than those prepared in hypothermic conditions. To determine the optimal slicing temperature, and further understand this cold-induced SD, we compared hippocampal brain slices of male CD-1 mice, prepared in aCSF at ~2°C, ~10°C, ~22°C and ~35°C. SD was induced in these slices by exposing them to oxygen-glucose deprived aCSF, and light transmittance imaging was used to visualize SD in the neocortex and hippocampus. Slice viability was judged by the latency to the onset of spreading depolarization, and by the change in light transmittance throughout SD propagation. Our results showed surprisingly little variation in the quality of brain slices prepared at either 2, 10 or 22 degrees Celsius. Slicing at ~35°C proved extremely difficult, due to the brain's lack of structural integrity when warmed. Our ongoing research is attempting to develop a protocol for best obtaining hippocampal brain slices at warm temperatures. However, results thus far have indicated that, although brain slices prepared below 5°C experience a 'cold SD' (Hancock et al., this meeting) its negative effects are likely outweighed by the cold's neuroprotective properties.

Disclosures: S.R. Wolkoff: None. **P.J. Gagolewicz:** None. **R.D. Andrew:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

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Topic: C.08. Ischemia

Support: NIH Grant R01NS121426
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Title: Guanosine is a rapid and dynamic neuromodulator in severe global ischemia

Authors: *M. E. WEESE-MYERS[1], M. T. CRYAN[1], C. E. WITT[1], K. C. N. CALDWELL[2], B. M. ARYAL[1], A. E. ROSS[1,2];
[1]Chem., [2]Neurosci., Univ. of Cincinnati, Cincinnati, OH

Abstract: Guanosine (GN) is a purinergic signaling molecule strongly implicated as a neuroprotective agent active across a wide range of neuropathologies. Its sister molecule adenosine has received significant attention for its role as a neuroregulator acting on a subsecond timescale to minimize damage during ischemic assault. Comparatively, GN's role as a rapid protective agent remains obscure. GN is of particular interest for its role as a modulator that acts preventatively to minimize excitotoxicity during ischemic assault. In the CA1 region of the hippocampus, which is particularly vulnerable to ischemic injury, high levels of glutamate and

dopamine (DA) accumulate in the extracellular space during ischemia. GN has been thoroughly established as a regulatory agent of glutamatergic excitotoxicity and is suggested to similarly upregulate DA reuptake in response to damage. Our lab has recently developed a method for subsecond detection of nanomolar levels of GN utilizing fast scan cyclic voltammetry. Here, we measure ms-to-s fluctuations in endogenous GN release during ischemic assault, providing a significant advancement in our understanding of the neurobiological role of purines during neuroprotection. We further investigate the potential regulatory role guanosine exerts on real-time dopamine release and reuptake and its impacts on oxidative stress in dopaminergic neurons. Transient GN and DA were monitored in hippocampal slices for 45 minutes and the amount released, the duration in the extracellular space, and the frequency of events were analyzed. Transient GN was verified pharmacologically with calcium deprivation and NTPDase1 inhibition. The effects of GN administration and its contributions through adenosine receptors on DA release in severe ischemia was also examined. Changes in cell morphology and mitochondrial stress were determined through immunohistochemical imaging. The effects of GN administration on the expression of NET and DAT transporters was examined with RT-qPCR and mitigation of oxidative stress in dopaminergic neurons through GN treatment was demonstrated with immunohistochemical imaging. We find that GN release amount and frequency are upregulated in ischemia and correlations between event duration and frequency suggest regulation through a high-threshold inhibitory autoreceptor. This is the first confirmation that guanosine is released on a subsecond timescale and that its signaling profile changes dynamically and immediately in response to ischemic assault. We also demonstrate for the first time that guanosine acts as a rapid regulator on dopamine during the early stages of ischemia.

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Poster

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Topic: C.08. Ischemia

Support: DGAPA-PAPIIT IN214723

Title: Axonal regeneration mediated by extracellular vesicles of neural stem cells in response to ischemia

Authors: *F. HERNÁNDEZ REAL[1], L. TOVAR-Y-ROMO[2];
[1]Inst. of Cell. Physiol., Natl. Autonomous Univ. of Mexico, Mexico City, Mexico; [2]Inst. of Cell. Physiol., Natl. Autonomous Univ. of Mexico, CDMX, Mexico

Abstract: Extracellular vesicles of neural stem cells mediate axonal regeneration inresponse to ischemia Fernando H. Real and Luis B. Tovar-y-RomoIschemic stroke is a leading

cause of mortality and disability. Various molecularfactors are triggered in response to stroke to promote tissue recovery, including theproliferation of neural precursors, mainly observed in murine models. Neural stemcells (NSCs) release extracellular vesicles (EVs) that contain factors capable ofpromoting neural recovery. This study investigated whether EVs shed from NSCisolated from the subventricular zone can enhance axonal regeneration after brainischemia. To address this question, we conducted a series of experiments *in vitro*where we established a model for assessing axonal growth following ischemia inmicrofluidic chips with cultured mouse hippocampal neurons exposed to NSC-EVs,and found that the administration of EVs isolated under normoxic conditions promoteaxonal recovery, using kymography as a proxy to axon functionality of theregenerated axons. We also monitored neuronal viability with flow cytometry andfound that treating neurons with EVs isolated from NSC cultured under normoxicconditions reduces the number of apoptotic and necrotic cells after ischemia.Interestingly, EVs obtained after oxygen and glucose deprivation exhibited noprotection, despite proteomic data indicating the presence of recovery-relatedproteins. These results indicate that it is plausible that some alternative signalingmolecules, such as regulatory RNAs, mediate these EVs' protective effect. Thesefindings are of great significance as EVs represent a novel therapeutic approach,and our data highlight their potential to promote post-ischemic recovery.Subsequently, our future research will focus on deciphering the underlyingmechanisms orchestrating the effects of EVs on axonal regeneration.This project was supported by DGAPA-PAPIIT IN214723

Disclosures: F. Hernández Real: None. **L. Tovar-y-Romo:** None.

Poster

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Topic: C.08. Ischemia

Support: NIH Grant NS100803

Title: Oligodendrocytic functional integrity relies on the apurinic/apyrimidinic endonuclease-1 for post-stroke recovery

Authors: J. BARREIRO[1], M. V. BREGY[2], Q. YE[3], W. ZHANG[1], *R. STETLER[4]; [2]Pittsburgh Inst. for Brain Disorders and Recovery, Neurol., [3]Neurol., [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Univ. Pittsburgh, Pittsburgh, PA

Abstract: BACKGROUND: The response of oligodendrocytes (OLs) to ischemic injury is not well understood, despite being a crucial element to ischemic injury and recovery. The critical DNA repair enzyme, apurinic/apyrimidinic endonuclease-1 (APE1) significantly impacts ischemic injury, but the specific contribution of APE1 in OLs following ischemia remains unknown. **AIM**: We wished to determine if OLs themselves require APE1 for cerebral ischemic recovery. **METHODS**: To address this issue, we generated mice with an OL-specific inducible

knockout of APE1 (OL-APE1 cKO) and subjected them to 60min transient middle cerebral artery occlusion (tMCAO). Immunohistochemistry, diffusion tension imaging, compound action potentials, and sensorimotor testing (accelerating rotarod, adhesive testing, cylinder test for lateral preference, and foot fault) were used for evaluation of histological, structural, and functional ischemic outcomes. Additionally, we crossed the OL-APE1-cKO mice with global knockout PARP mice to determine the role of PARP in potentiating or improving on APE1-cKO deficits. **RESULTS**: Acute (pre-ischemic) knockout of APE1 in OLs increased the acute presence of DNA damage and stress signaling in OLs. Using histology, MRI, and electrophysiology, we found increased disruption of white matter tract integrity and function in OL-APE1 cKO ischemic mice compared to ischemic genotype controls. In addition, sensorimotor outcomes were impaired in OL-APE1 cKO mice compared to ischemic genotype controls. Crossing the OL-APE1-cKO mice with the global PARP KO mice did not significantly affect sensorimotor outcomes after stroke. Together with our previous work, these data suggest that not just neurons, but also oligodendrocytes require APE1 for functional recovery after cerebral ischemic injury and that PARP is not likely involved in functional deficits observed in OL-APE1-cKO ischemic mice.

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Poster

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Topic: C.08. Ischemia

Support: NINDS R01NS075930
NINDS U24NS119100

Title: Astrocyte - Neuron Differential Vulnerability in Brain Following Middle Cerebral Artery Occlusion

Authors: L. ECKSTEIN[1], A. BROOKSHIER[1], H. CHANG[1], S. LISKA[1], W. ALTON[1], *P. LYDEN[1,2];
[1]Physiol. and Neurosci., USC, Los Angeles, CA; [2]Neurol., USC, Los angeles, CA

Abstract: In mammalian brain, cell types (neurons, glia, endothelial cells, pericytes) are organized into a neurovascular unit. During ischemia, cells farthest from the blood supply die first: neurons before astrocytes before vasculature, a process known as ‘selective vulnerability.’ In contrast, using in vitro pure cell-type cultures we found that astrocytes tolerate oxygen-glucose deprivation far longer than brain endothelial cells or pericytes, which survive longer than neurons (Rajput 2018 Glia: DOI: 10.1002/glia.23714), a process we call ‘differential vulnerability’. Here we sought to find evidence supporting differential vulnerability in vivo. We

used equal numbers of male and female Sprague Dawley rats aged 3-4 months, in a standard nylon filament model of middle cerebral artery occlusion (MCAo). Animals were randomly assigned to 2, 4, 6 or 12 hours of MCAo followed by 30 minutes reperfusion and then cardiac perfusion with 4% paraformaldehyde. Animals were rated using a 4-point behavioral deficit scale (0=normal, 3 = most severe, Bederson) at occlusion and again at the end of reperfusion. After immersion fixation and dehydration in sucrose, 25µm thick sections were cut using a freezing microtome; mounted on gelatin subbed slides; stained with Sytox Red, anti-GFAP, anti-NeuN, and anti-Tie2. For this study we selected one section per brain in the mid-parietal cortex (Bregma+1.0mm). Three z-stacks were imaged in each of three cortical regions: stroke, ipsilateral cingulate, and contralateral cortex homotopic to the stroke region. One examiner blind to occlusion durations counted all profiles that were positive for each marker; cell death was expressed as the ratio of Sytox+ to total cell-type marker positive cells. After all cell counts were completed, we then excluded subjects with deficit rating scores < 3. We found no significant differences in cell death numbers among cell types in contralateral and ipsilateral cingulate cortex. In stroke cortex, Sytox+/NeuN+ profiles exceeded Sytox+/GFAP+ profiles at all time points (ANOVA with Dunnett's post-hoc correction, $p<0.01$.) With increasing duration of MCAO, Syto+/NeuN+ profile ratios reached maximum after 4 hours, but Sytox+/GFAP+ ratios did not maximize until 12 hours. The Sytox+/GFAP+ ratios over 2, 4, 6, and 12 hours were (%, mean±SD) respectively: 1.1±2.9, 30.3±28.9, 29±32.4, and 69±27, while for Sytox+/NeuN+ profiles, ratios were 21.5±23, 72.97±19.9, 68.8±20.5, and 59.6±10. These data are consistent with differential vulnerability in vivo, as we defined it in vitro. Differential vulnerability is an inherent property of brain cell types that determines survival after ischemia.

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Poster

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Japan Society for the Promotion of Science grant 22J23169

Title: Novel lipid metabolites trigger brain-autonomous neural repair after ischemic stroke.

Authors: *A. NAKAMURA[1], S. SAKAI[2], M. MURAKAMI[3], T. SHICHITA[1];
[1]Tokyo Med. and Dent. Univ., Yushima, Japan; [2]Stroke Renaissance Project, Tokyo Med. and Dent. Univ., Tokyo, Japan; [3]The Univ. of Tokyo, Bunkyo-ku, Japan

Abstract: Stroke is a major cause of disability worldwide. Since rehabilitation promotes functional recovery after brain injury, the brain has endogenous self-recovery mechanisms triggering a broad range of neural repair that have not been identified. By the comprehensive study of phospholipid metabolites and their generating enzyme, phospholipase A2 (PLA2), we have identified the pivotal enzyme and phospholipid metabolites for functional recovery after ischemic stroke. Through this lipid metabolism, the endogenous molecular mechanisms triggering a broad range of neural repair were investigated by single-cell RNA-seq analysis of peri-infarct neurons collected from the murine ischemic brain after transient middle cerebral artery occlusion (MCAO). We have identified dihomo-γ-linolenic acid (DGLA) and its metabolites generated by PLA2G2E, a secreted PLA2 from peri-infarct neurons, as essential for functional recovery. Poor functional prognosis in Pla2g2e-deficient mice was explained by the loss of peptidyl arginine deiminase 4 (Padi4) in peri-infarct neurons. Single-cell RNA-sequencing analysis demonstrated that Padi4 was pivotal for the transcriptional regulation in peri-infarct neurons to promote survival and neural repair. The administration of DGLA and its metabolites induced Padi4 in the peri-infarct neurons and accelerated functional recovery after ischemic stroke. Thus, our research clarifies the promising potential of brain-autonomous neural repair triggered by the specialized lipids that initiate self-recovery processes after brain injury.

Disclosures: A. Nakamura: None. **S. Sakai:** None. **M. Murakami:** None. **T. Shichita:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.18/O5

Topic: C.08. Ischemia

Support: NIH grant 1R35NS132184-01

Title: Long noncoding RNA AK020504 knockdown exacerbates ischemic brain injury

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Abstract: The dynamics of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) on DNA constitute a major epigenetic modification in the CNS, critically regulating neuronal homeostasis. We previously showed that conversion of 5mC to 5hmC by the enzyme ten-eleven translocase 3 (TET3) induces transcription of several neuroprotective genes and confers resilience to ischemic brain injury in mice. Interestingly, TET3 neuronal isoform lacks a DNA binding domain, and the mechanism by which TET3 binds to DNA to promote 5hmC-mediated transcriptional induction in the post-stroke brain is yet unknown. Long noncoding RNAs (lncRNAs) act as structural scaffolds to recruit chromatin-modifying agents. In the present study,

TET3-bound intergenic lncRNAs were identified by RNA pull-down from mouse brain. One of those lncRNAs known as AK020504 with ~80% homology to humans is significantly upregulated in the peri-infarct cortex of mice subjected to transient middle cerebral artery occlusion (MCAO). Hence, we tested the functional significance of AK020504 in regulating secondary brain damage after stroke. AK020504 knockdown significantly increased the infarct volume and worsened the post-stroke motor function recovery following MCAO. Our studies showed that TET3 activation by ascorbate decreases the infarct volume and promotes better motor functional recovery after stroke in mice. Interestingly, AK020504 knockdown counteracted the protective effects of ascorbate after transient MCAO. When mice were treated with AK020504 siRNA + ascorbate, they showed increased infarct volume and decreased motor function recovery compared to the ascorbate-treated group. At the molecular level, AK020504 inhibition significantly curtailed the 5hmC levels. These results indicate that lncRNA AK020504 may be essential for TET3-mediated 5hmC-dependent epigenetic reprogramming in the post-stroke brain.

Disclosures: V. Arruri: None. **K. Morris-Blanco:** None. **R. Vemuganti:** A. Employment/Salary (full or part-time):; William S. Middleton Veterans Administration Hospital, Madison, WI, US.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.19/O6

Topic: C.08. Ischemia

Support: KAKENHI 17K10846
KAKENHI 22H03441
SENSHIN Medical Research Foundation
Taiju Life Social Welfare Foundation
Japan Brain Foundation

Title: Effect of Ezh2 knockdown on postischemic neurogenesis in gerbil hippocampus

Authors: *Y. SEHARA[1], R. WATANO[1], K. OHBA[1], K. SHIMAZAKI[2], K. KAWAI[2], H. MIZUKAMI[1];
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Abstract: Introduction: Neurogenesis persists during the whole life in the subgranular zone of dentate gyrus in hippocampus. Neurogenesis of subgranular zone generates only granule cells. This neurogenesis increases after brain insults including ischemia and trauma. On the other hand, neurogenesis decreases in Alzheimer disease and meningitis. These phenomena should be intriguing, however, the mechanisms of neurogenesis have not been elucidated.

Purpose: This study focuses on the relationship between polycomb group complex (PcG) and neurogenesis after transient ischemia, which is known to regulate gene silencing through histone methylation.
Methods: We made adeno-associated virus (AAV) vector carrying small interfring RNA (siRNA) targeting Ezh2, which is a core component of PcG. For the control group, nontargeting (NT) siRNA was also prepared. Four-week-old male gerbils were injected with 3.4×10^{10} viral genomes of AAV vector into the right hippocampus. At the age of 6 weeks, the animals were operated with transient occlusion of bilateral carotid arteries for 5 mins. At the age of 7 weeks, the animals were injected with 5-Ethynyl-2'-deoxyuridine (EdU, 50 mg/kg body weight, twice) intraperitoneally to label proliferating cells. At the age of 9 weeks, the animals were decapitated for the histological analysis (N = 5, each group).
Results: In the dentate gyrus, the number of EdU-positive cells in the NT siRNA + ischemia group was significantly increased compared to the control ($p < 0.001$). Furthermore, Ezh2 siRNA + ischemia group showed significantly smaller number of EdU-positive cells, compared to NT siRNA + ischemia group ($p < 0.05$) (Control: 20.4 ± 3.1; NT siRNA + sham: 14.8±1.4; Ezh2 siRNA + sham: 17.0±2.2; NT siRNA + ischemia: 64.2±6.1; Ezh2 siRNA + ischemia: 32.8±5.8). Next, the number of Sox2-positive cells in the subgranular zone was quantified, which is a neural stem cell marker. The number of Sox2-positive cells decreased in the NT siRNA + ischemia ($p < 0.05$) and Ezh2 siRNA + ischemia groups ($p < 0.01$), compared to the control group (Control: 333.8 ± 23.9; NT siRNA + sham: 309.4 ± 7.7; Ezh2 siRNA + sham: 324.4 ± 16.5; NT siRNA + ischemia: 242.0 ± 34.5; Ezh2 siRNA + ischemia: 210.4 ± 10.2).
Conclusions: Ischemic insult increased neurogenesis in the dentate gyrus of hippocampus. Ezh2 reversed the post-ischemic increase of neurogenesis in the gerbil dentate gyrus.

Disclosures: Y. Sehara: None. **R. Watano:** None. **K. Ohba:** None. **K. Shimazaki:** None. **K. Kawai:** None. **H. Mizukami:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.20/O7

Topic: C.08. Ischemia

Support: NIH-NINDs Grant R01NS116143

Title: Determining the connection between stroke and Alzheimer's Disease in iPSC derived cortical neurons

Authors: *E. POTTS[1], B. CHATRAGADDA[2], C. FALLINI[2];
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Abstract: Ischemia is a life-threatening condition resulting from medical emergencies like stroke. Lack of oxygen and glucose during stroke leads to acute neuronal death and long-lasting

damage to affected brain regions. Having a stroke also greatly increases an individual's risk of developing Alzheimer's Disease later in life. During stroke neurons experience acute ischemia, which impacts the actin cytoskeleton through aggregation of actin and cofilin, formation of actin stress fibers, and neurofilament destabilization. RNA-binding proteins (RBPs) then begin to accumulate in the cytoplasm, similar to the pathology seen in neurodegenerative disorders. However, the molecular link between ischemia-induced cellular changes and neurodegeneration is unclear. Our previous research has established a link between actin homeostasis and the functional stability of the nuclear pore complex (NPC). Thus, we hypothesize that rearrangement of the actin cytoskeleton after stroke may have long-term impacts on the NPC, leading to the mislocalization and aggregation of nuclear proteins with downstream effects on gene regulation. To test this, we expose iPSC-derived cortical neurons to acute oxygen and glucose deprivation (OGD) followed by a recovery period under normal oxygen and glucose conditions. We examine changes to nuclear structures, the cytoskeleton, gene regulatory proteins, and alterations to splicing patterns. Our results show that acute ischemia induces long-lasting changes that affect the localization, abundance, and function of regulatory proteins. Our research will yield novel insights into early changes occurring after a stroke that may lead to an increased risk of AD.

Disclosures: **E. Potts:** None. **B. Chatragadda:** None. **C. Fallini:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.21/O8

Topic: C.08. Ischemia

Support: NIH R01NS058784

Title: Spatial mapping of stem cell-induced transcriptional alterations in stroke-injured rat brains

Authors: ***P. HABIB**[1], Y. ZATULOVSKAIA[1], X. LIANG[1], F. DU[1], S. TIGCHELAAR[1], C. DONG[1], M. WINTERMARK[2], T. M. BLISS[1], G. K. STEINBERG[1];
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Abstract: Human neural stem cell (hNSC) therapy for chronic disabilities resulting from ischemic stroke is showing promise as it moves into clinical trials. In our previous phase 1/2a study using SanBio bone marrow derived stem cells, 75% of patients exhibited a transient T2-FLAIR (fluid-attenuated inversion recovery) MRI signal in the premotor cortex around the needle track following intraparenchymal stem cell transplantation (tx) in the chronic phase of stroke. Notably, the size of this FLAIR signal positively correlated with the extent of motor recovery, suggesting that the underlying cellular and molecular mechanisms in this FLAIR region could drive stroke recovery. Translating from bedside back to bench, we replicated the tx-induced FLAIR signal following chronic stroke in adult male Sprague Dawley rats subjected to

30 min of transient middle cerebral artery occlusion followed 1 month later by transplantation of embryonic derived neural stem cells or buffer into the ipsi-lesional striatum. To study the effect of stem cells/vehicle on neurological outcomes and the extent of T2-FLAIR, Whisker paw test and different MRI sequences (T2w, T1, FLAIR, DWI) were performed at multiple time points. For an unbiased spatially resolved whole transcriptome analysis we utilized the Visium platform from 10X genomics; for this exploratory pilot study, we examined two stem-cell and two vehicle-treated brains at the peak of T2-FLAIR (1d post-tx). Consistent with our clinical observation, we found a positive correlation between FLAIR and improved neurological outcomes in the chronic phase after stroke. Spatial transcriptomics identified specific gene signatures for the stroke-injury, transplant/needle-track, stem cell graft, and the cortical 'FLAIR' region. The latter consisted of two components, a central core containing the gene signature of the needle track and blood, and a wider region around this core which encompasses the FLAIR lesion seen by MRI. This wider FLAIR region displayed a predominantly microglia/inflammation-associated signature and was best characterized by the upregulation of apoptosis-associated genes. Pathway analysis of the differentially-expressed genes in the FLAIR cluster suggested a significant representation of immune cell responses such as phagocytosis, immune cell migration, and cytokine signaling, in addition to the activation of unfolded protein response/ER-stress mechanisms.
Our study provides the first evidence for an altered immune response in the recovery-associated transplant-induced FLAIR region. Further studies will help increase our understanding of how stem cells promote brain recovery.

Disclosures: P. Habib: None. **Y. Zatulovskaia:** None. **X. Liang:** None. **F. Du:** None. **S. Tigchelaar:** None. **C. Dong:** None. **M. Wintermark:** None. **T.M. Bliss:** None. **G.K. Steinberg:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.22/P1

Topic: C.08. Ischemia

Support: Office of Naval Research Award N000141712644
NIEHS Grant U01 ES028184

Title: Characterization of Ischemia with Reperfusion in a Three-Dimensional Cortical Spheroid Model

Authors: *I. TOP[1,2], R. M. MCLAUGHLIN[1,2], D. HOFFMAN-KIM[1,2,3,4];
[1]Dept. of Neurosci., [2]Robert J and Nancy D Carney Inst. for Brain Sci., [3]Ctr. for Biomed. Engin., [4]Ctr. for Alternatives to Animals in Testing, Brown Univ., Providence, RI

Abstract: The conflicting clinical findings involving patients receiving reperfusion after cerebral ischemia warrant future research. Three-dimensional in vitro models offer a high-throughput approach to studying brain injury while mimicking the brain microenvironment. Here, a self-assembled, scaffold-free 3D in vitro cortical spheroid model was used to explore the effects of ischemia-reperfusion injury on metabolic activity and cell morphology. P0-2 rat cortices were used to seed spheroids at 4000 cells/spheroid. On day 13, we exposed spheroids to 24 hours of oxygen-glucose deprivation (OGD) with reperfusion (OGD+R) for 24, 48, or 72 hours. For OGD, we placed spheroids in an anaerobic chamber with glucose-free media. For reperfusion, spheroids were re-exposed to 5% CO2 and media with glucose. ATP content was reduced after OGD relative to control ($p<0.001$) and after each OGD+R timepoint compared to their age-matched controls ($p<0.001$) (n=24 spheroids per group across three replicates, mixed model analysis, Tukey HSD). Relative ATP content decreased after OGD, increased at OGD+24R, and decreased at the OGD+48R and OGD+72R timepoints. Spheroids showed injured neurite cytoskeletons after OGD in the form of B-3-tubulin positive puncta and loss of intact structures. After OGD, 23/35 spheroids were injured, with 13/32 at OGD+24R, 10/33 at OGD+48R, and 12/32 at OGD+72R. OGD spheroids showed hypertrophic astrocytes with increased glial fibrillary acidic protein voxel intensity (704.01 ± 3.06, mean ± SEM) compared to control (550.18 ± 2.62, $p<0.001$). There was some recovery in astrocyte reactivity at OGD+24R (549.19 ± 1.41) compared with its age-matched control ($p=0.573$), with an increase in astrocyte reactivity at OGD+48R (611.79 ± 2.67, $p<0.001$) and OGD+72R (611.00 ± 2.26, $p=0.012$) compared to their respective age-matched controls (n=10 spheroids per group, one-way ANOVA analysis, Tukey HSD). Together, these results showed a pattern of recovery at 24 hours of reperfusion, which then decreased at the 48 and 72 hours. This high-throughput, reproducible 3D model allowed us to investigate the impact of reperfusion on cell viability and morphology across a range of clinically relevant timepoints in an in vivo-representative microenvironment. Reperfusion therapies are necessary to prevent ischemic tissue from progressing into further infarction and to allow for tissue recovery after stroke. Future studies will focus on characterizing the pathophysiological mechanisms and changes in different cell types within the spheroids, as well as screening novel therapeutics to alleviate the damage inflicted by reperfusion injury.

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Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.23/P2

Topic: C.08. Ischemia

Support: JSPS KAKENHI Grant Number 23K14308
Hyogo Medical University Diversity Grant for Research Promotion

Title: Induction of Nrf2 converted brain pericytes to neural stem cells

Authors: *R. SAKUMA, Y. MINATO, S. MAEDA, H. YAGI;
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Abstract: Brain pericytes are a mural support cell population elongated at intervals along the walls of capillaries. It has been proposed that they have multipotency in response to tissue injury and contribute to the regenerative process. Using a C.B-17 mouse model of ischemic stroke, normal brain pericytes (nPCs) are converted to ischemic pericytes (iPCs), some of which function as multipotent stem cells. We investigated the mechanism of the PC reprogramming phenomenon. In our previous report, we revealed that oxygen-glucose deprivation (OGD) in nPCs promoted mesenchymal-epithelial transition. Sox2 and nestin, which are neural stem cell markers, were highly expressed in iPCs. The expression of *Sox2* mRNA increased in nPCs under OGD condition, however, *nestin* mRNA was not induced. We investigated whether nPCs acquire stemness under OGD/Reoxygenation (OGD/R), a mimicked oxidative stress. nPC-OGD/R treatment induced *nestin* and *Sox2* mRNA expression. Comparative analysis of the traits of nPCs and iPCs showed that *nestin* and *Sox2* mRNAs and intercellular levels of reactive oxygen species (ROS) were more highly expressed in iPCs than in nPCs. In addition, nuclear factor erythroid-2-related factor 2 (Nrf2), a key player in antioxidant defenses, was detected in the nucleus of iPCs. These results lead us to hypothesize that Nrf2 induction in response to oxidative stress is a key for the acquisition of neural stemness following ischemia. The expression of *nestin* and *Sox2* mRNA was also upregulated by tBHQ treatment, a Nrf2 inducer, or Nrf2 overexpression. Furthermore, Nrf2-overexpressing PCs formed neurosphere-like cell clusters and could differentiate into Tuj1-positive neurons. In conclusion, we suggested that the conversion of nPCs into iPCs was regulated by an antioxidant system, and the targeting of Nrf2 has emerged as a novel therapeutic strategy for the repair of CNS diseases. Although the exact molecular mechanism of Nrf2 induction and acquisition of stemness remains unclear, we believe that Nrf2 in iPCs was phosphorylated. pNrf2 mediates neuroprotective effects on ischemic stroke and we also detected the expression of pNrf2 in the nucleus of iPCs using pNrf2 (Ser40) antibody. Our future studies will offer novel therapeutic strategies for ischemic stroke by revealing the signaling pathway of pNrf2 that induces the acquisition of stemness.

Disclosures: **R. Sakuma:** None. **Y. Minato:** None. **S. Maeda:** None. **H. Yagi:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.24/P3

Topic: C.08. Ischemia

Title: Neuroprotective Roles of HAX-1 in Ischemic Neuronal Injury

Authors: *H. YOSHIOKA, X. SUI, T. WAKAI, K. HASHIMOTO, T. TATEOKA, R. HORIUCHI, H. KINOUCHI;
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Abstract: Hematopoietic cell-specific protein 1 associated protein X-1 (HAX-1) is a novel mitochondrial protein that regulates oxidative stress-induced apoptosis. However, the roles of HAX-1 in ischemic neuronal injury have not been thoroughly elucidated. In this study, the expression and roles of HAX-1 after ischemic stress were investigated using *in vivo* and *in vitro* models. The effect of oxidative stress on the regulation of HAX-1 was examined using knockout mice lacking nicotinamide-adenine dinucleotide phosphate oxidase (NOX), which is a major source of reactive oxygen species (ROS) after cerebral ischemia. Male C57BL/6J mice were subjected to transient forebrain ischemia induced by 22-minute occlusion of the bilateral common carotid arteries, and striatum samples were analyzed. For *in vitro* ischemic experiments, oxygen and glucose deprivation (OGD) in a rat pheochromocytoma cell line was utilized. Western blotting and immunofluorescence analysis revealed HAX-1 expression in neuronal mitochondria, which was significantly decreased after ischemia *in vivo* and *in vitro*. The ischemia-induced decrease in HAX-1 expression in NOX knockout mice was significantly inhibited compared to that in wild-type mice. Inhibition of HAX-1 using small interfering RNA significantly increased injury in cultured cells after OGD. These findings suggest that HAX-1 has a neuroprotective effect against ischemic neuronal injury, and downregulation of HAX-1 by NOX-produced ROS induces apoptosis after cerebral ischemia.

Disclosures: H. Yoshioka: None. **X. Sui:** None. **T. Wakai:** None. **K. Hashimoto:** None. **T. Tateoka:** None. **R. Horiuchi:** None. **H. Kinouchi:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.25/P4

Topic: C.08. Ischemia

Support: Diversity Supplement NS046072
AHA Predoctoral Fellowship

Title: Sex and Circuit Specific Amygdala Dysfunction After Global Cerebral Ischemia

Authors: *J. J. VIGIL[1], E. TIEMEIER[2], N. E. CHALMERS[1], P. S. HERSON[3], N. QUILLINAN[4];
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Abstract: Modern medical advances have increased the odds of surviving an ischemic event such as cardiac arrest or stroke. With more people surviving and recovering from these ischemic insults, it is increasingly apparent that survivors experience long-term effects on brain function. We have previously identified cognitive dysfunction in a mouse model of global cerebral ischemia (GCI) which is attributed to hippocampal neurodegeneration and impaired hippocampal

plasticity. However, no study has attempted to identify amygdala dysfunction after GCI, despite clinical evidence of emotional dysfunction, such as anxiety and PTSD. Therefore, it is important to identify the effect that GCI has on the amygdala, the emotional center of the brain. I hypothesize GCI induces dysfunction of L-type calcium channels (LTCCs) within the basolateral amygdala (BLA) thereby contributing to deficits in amygdala-dependent behavior and LTP in male mice. Experimental GCI was induced in adult (8-12 week) C57BL6 mice via cardiac arrest and subsequent cardiopulmonary resuscitation (CA/CPR). CA was induced for 8-minutes and subsequent resuscitation by epinephrine injection, ventilation, and mild chest compressions. 7-days post GCI, the amygdala-dependent delay fear conditioning paradigm was used to assess amygdala-dependent learning and memory. Synaptic plasticity was evaluated by performing LTP recordings in the BLA, and LTCC function was assessed using whole-cell voltage clamp recordings. Neuronal injury was evaluated at 3-days post CA/CPR by Fluorojade staining. Behavioral testing revealed that only male mice are diminished in their ability to form associative memories (52.4% sham freezing vs 26.6% in CA/CPR). Similarly, plasticity of the cortical inputs to the BLA are impaired only in males (143.6% of baseline in controls vs 110.9% of baseline in CA/CPR). Interestingly intra-amygdala recordings revealed no disruption of LTP in this circuit and we observed no cell death within the BLA of either sex. Whole-cell LTCC mediated currents were minimally affected by GCI, however, additional 2-photon calcium imaging experiments will evaluate LTCC function at more distal synapses after GCI. These results support the role of the amygdala in cognitive-affective impairments after CA despite a lack of neuronal cell death in this brain region. We have revealed a sex and circuit specific deficit in amygdala function that provides new insights into the role that biological sex plays in mediating brain dysfunction following CA. We will continue to unravel the mechanisms by which this sexually dimorphic impairment occurs.

Disclosures: **J.J. Vigil:** None. **E. Tiemeier:** None. **N.E. Chalmers:** None. **P.S. Herson:** None. **N. Quillinan:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.26/P5

Topic: C.08. Ischemia

Support: R01 NS075930 (PI)

Title: Investigating the differential expression of metabolites in the Neurovascular Unit following ischemic-reperfusion injury.

Authors: *A. BROOKSHIER, P. LYDEN;
USC, Los Angeles, CA

Abstract: Preclinical assessment of new stroke treatments typically emphasizes neuronal salvage, but no neuron-specific protectant has yet succeeded in clinical stroke trials. We have previously demonstrated that each cell type responds uniquely to conditions of stress (e.g., substrate deprivation) and drug treatments in vitro. The objective of this study was to gain a greater insight on the cell-type-specific responses during cerebral ischemia. We used oxygen-glucose deprivation (OGD) in primary monocultures of neurons, astrocytes, endothelial cells, and pericytes. A standard filament MCAo model was used in mice and rats. Each NVU cell type was cultured for OGD, n = 6 wells per time point. Astrocyte cultures tolerated OGD for many hours, with a 50% lethal dose rate (LD 50) of 6 hours, endothelial and pericyte LD 50 4 h, and neuron LD 50 1.5 h ($p < 0.0001$ across all cell types). Bulk RNA sequencing was performed on astrocyte and neuronal cultures under normal conditions and OGD (LD 50). The three differentially expressed genes of interest in the tricarboxylic acid cycle (TCA) were *ogdh* (neuron 0.439, $p< 0.496$; astrocyte 2.772, $p< 0.0005$), *dslt* (neuron, -1.332, $p < 0.324$; astrocyte, -1.9120, $p < 0.331$), and *cs* (neuron, 0.549, $p < 0.780$; astrocyte, -2.069, $p< 0.158$). The three differentially expressed genes of interest in glycolysis were *eno2* (neuron, -3.155, $p < 0.0002$; astrocyte, 0.158, $p < 0.008$), *aldoc* (neuron, -3.876, $p< 0.08$; astrocyte, 2.65, $p < 0.821$), *pgm2* (neuron, 0.694, $p< 0.593$; astrocyte, 1.688, $p< 0.262$). The three differentially expressed genes of interest in glycogen metabolism were *pygb* (neuron, NA; astrocytes, 0.898; $p< 0.826$), *pygl* (neuron, -1.04, $p< 0.0002$; astrocyte, 0.378, $p < 0.006$), and *gys2* (neuron, -4.298, $p< 0.006$; astrocyte, 0.898, $p< 0.026$). These findings have revealed differences in the metabolic profiles between the cell types and potential targets for studying cell-type-specific responses to ischemia. Future work includes determining the role glycogen metabolism has in astrocyte tolerance to ischemia through the inhibition and induction of key enzymes, like glycogen phosphorylase (Pygb) and glycogen synthase (Gys2) in the NVU. Elucidating the cell-type specific behaviors to ischemia will provide insight for and improve future therapeutic development.

Disclosures: **A. Brookshier:** None. **P. Lyden:** None.

Poster

PSTR077. Ischemia: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.27/P7

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Finnish Red Cross Blood Service Research Fund Grant 2021
Finnish Cultural Foundation, Pirkanmaa Regional Fund
the Academy of Finland, the Center of Excellence in Body-on-Chip Research 336665

Title: Uptake of clinically relevant human platelet secreted extracellular vesicles into human induced pluripotent stem cell derived neurons in hypoxic conditions

Authors: *V. HARJU[1], K. HÄRKÖNEN[2], U. IMPOLA[2], S. LAITINEN[2], S. NARKILAHTI[1];
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Abstract: Brain stroke is one of the leading causes of death and disability worldwide. However, the current treatments have limited time window and low regeneration potential. During ischemic stroke, neurons in the hypoxic core region are dying, but the ones in penumbra area have potential to recover. We have differentiated human induced pluripotent stem cells (hiPSC) into neurons and used this in vitro model to study the effects of hypoxia to the neurons. We have studied hypoxia induced alterations in neuronal morphology with immunocytochemical staining and neuronal functionality with microelectrode array (MEA). After 24 h in 1% hypoxic conditions, neurons had more fragmented neurites and showed less neuronal activity. Both neuronal spiking and bursting were decreased. However, during reperfusion the activity recovered. Besides studying the effects of hypoxia, we have tested potential treatment method of human platelet derived extracellular vesicles (EVs). Neuronal uptake of Carboxyfluorescein succinimidyl ester (CFSE)-labeled EVs was confirmed with confocal imaging and further analysis with Imaris software. Results showed neuronal uptake of EVs and their localization into cellular organelles was verified. Here, we have generated in vitro model to study transient stroke and showed that neurons can uptake platelet derived EVs. Together, our findings are advancing the non-animal research of human brain stroke.

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Poster

PSTR078. Assessment and Imaging of Stroke

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Program #/Poster #: PSTR078.01/P8

Topic: C.09.Stroke

Support: U-GOV CALE_ECCE19_01

Title: Investigation of putative neuronal biomarkers for recovery in a mouse model of stroke

Authors: *L. VIGNOZZI[1], S. VARANI[1], E. BERETTA[1], A. LEPARULO[1], S. VASSANELLI[1,2], G. DEIDDA[1,2], M. ALLEGRA[2,3,4];
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Abstract: Ischemic stroke is a neurological injury caused by the occlusion of cerebral blood vessels and represents one of the major causes of adult disability worldwide. During the so-called "critical period" following an ischemic event, neural circuits in the peri-infarct zone undergo plastic changes that can lead to the recovery of the impaired neurological function. However, the extent of the spontaneous recovery among patients remains highly variable, only

partially depending on structural and functional factors related to the damage, such as lesion size and location, and the connectivity of neural circuits. Therefore, identifying neurophysiological biomarkers for early prediction of the evolution of the recovery is an essential tool for the treatment of this pathology. To address this aim, we used a well-established mouse model of stroke, the middle cerebral artery occlusion (MCAO) in adult mice (2 to 5 months old) and evaluated the recovery outcome at different days (D) after stroke induction (D2, D9, and D30). Specifically, we behaviorally assessed the motor function recovery using the gridwalk test and we found higher motor deficits in stroke mice (n=16) compared to controls (n=12; Two Way RM Anova, $p<0.001$). To explore whether the recovery outcome of each animal could correlate with neural changes of the intra-hemispheric connectivity, we performed *in vivo* local field potential (LFP) recordings in anesthetized Thy1-ChR2-YFP transgenic mice at D9 and D30, the subacute and chronic phases of stroke, respectively. Evoked LFPs were recorded from the peri-infarct zone, i.e. the forelimb primary motor cortex (caudal forelimb area, CFA) in response to the optogenetic stimulation of the ipsilateral pre-motor cortex (rostral forelimb area, RFA). Specifically, the amplitude, the time of the peak, and the area under the curve of the responses at different stimulation intensities (3mW, 5mW, half power of the maximum response) were considered in the analysis as a proxy for plastic changes. We found higher amplitude responses to intra-hemispheric photostimulation in stroke mice with good recovery outcome (n=9) compared to those with low motor recovery (n=7) at D30 after stroke (t-test, $p<0.05$). Overall, our results suggest that a greater neural plasticity of the intra-hemispheric connectivity may underlie the good recovery outcome of the motor function, thus opening new perspectives for further preclinical investigations.

Disclosures: L. Vignozzi: None. **S. Varani:** None. **E. Beretta:** None. **A. Leparulo:** None. **S. Vassanelli:** None. **G. Deidda:** None. **M. Allegra:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.02/P9

Topic: C.09.Stroke

Support: Exploratory Research Seed Grant funding from the OHSU School of Medicine

Title: Mri modalities characteristics of selective subcortical white matter ischemic injury correlates with behavioral deficits

Authors: *H. NGUYEN, M. PIKE, S. BALTAN;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: White matter injury (WMI) is associated with disabilities after stroke, and the mechanisms of WMI differ from gray matter. Our previous *in vitro* studies demonstrated casein

kinase 2 (CK2), a master kinase, is upregulated in WM after ischemic injury causing impaired axonal function and mitochondrial disruption. We found that CX-4945, an FDA-approved CK2-specific and selective inhibitor, promotes axon function recovery by conserving mitochondria. However, whether CK2 inhibition conserves mitochondrial dynamics to confer similar protection in a selective WMI *in vivo* model remains to be tested. We evaluated the effects of CX-4945 using a selective WMI *in vivo* model by assessing the axon functional and structural integrity. We also developed MRI modalities to characterize the injury to correlate with behavioral deficits. Using 2-month-old C57BL/6 males, three injections each of 200 nL of L-NIO (130µM) or saline for sham were deposited at the previously identified coordinates. 12 hours after WMI, the control group were administered saline and the treatment group with CX-4945 (75mg/kg) for 5 days, twice daily. Behavioral deficits were assessed using cylinder test, and pasta eating test at baseline, day 1, 7, 21 and 28 post-injury. T2-weighted imaging and diffusion tensor imaging (DTI) of the mice were taken on days 2 and 10 post-injury to assess WM changes in corpus callosum (CC). WM integrity was assessed histologically using NF160/200+ neuro-filament marker, MBP+ myelin, Olig2+ oligodendrocytes, GFAP+ astrocytes, Iba-1+ microglia. Mitochondrial dynamics related-proteins Mfn-1, Mfn-2, Drp-1, and OPA-1 were quantified. Using DTI and T2-weighted MRI scans, we detected a reduction FA signaling in the ipsilateral CC and a persistent focal edema without significant changes in volume. These imaging modalities correlated with behavioral deficits. Injured mice showed a biased use of the contralateral paw over the bilateral paw and increase eating time. Post-ischemic administration of CX-4945 improved bilateral paw use, motor coordination, and maintained paw dexterity. Moreover, treatment with CX-4945 preserved NF160/200+, MBP+, Olig2+ intensity signals while decreases GFAP+ and Iba-1+ signals. We established the selective subcortical WMI *in vivo* model that causes significant focal damage CC. WMI can be detected using MRI indicated by local edema and reduction in FA. WMI is confirmed with histological assessment and is correlated with behavioral deficits. CX-4945 exerted post-ischemic protection of axon, oligodendrocytes, and myelin and effectively alleviated behavioral deficits by preserving mitochondrial dynamics in young male mice.

Disclosures: **H. Nguyen:** None. **M. Pike:** None. **S. Baltan:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.03/P10

Topic: C.09.Stroke

Support: RFAG042189
RF1NS119872

Title: Prior-social isolation affects stroke outcomes in a sex-dependent manner

Authors: *M. E. ZARDENETA[1], T. BRANYAN[2], F. SOHRABJI[3];
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Abstract: Introduction: Stroke is a leading cause of disability and long-term motor and language impairment, leading to decreased quality of life. Patients often experience social isolation after stroke due to persistent disability and/or post-stroke changes in mood and affect. Experimental studies show that post-stroke social isolation delays recovery. Considering the long periods of social distancing imposed by the COVID-19 pandemic, it is likely that prior-social isolation (SI) might also significantly affect stroke outcomes. We aim to elucidate the physiological effects of SI and subsequent vulnerability to stroke. We hypothesize that prior-social isolation will increase stroke severity in middle-aged rats due to increased neuroinflammation. **Methods:** Middle-aged male and female rats were single (socially isolated; SI) or double housed for 5 weeks and then subjected to middle cerebral artery occlusion via the endothelin-1 stroke model. Rats were terminated 5 days post-stroke, and infarct volume, survival, and sensorimotor performance were assessed. Serum was analyzed for levels of inflammatory cytokines and the bacterial metabolite lipopolysaccharide (LPS). **Results:** SI showed a trend towards increased stroke-induced mortality ($p=0.058$) in females but not males. Infarct volume in surviving SI females was increased compared to SI males ($p=0.0181$). No significant difference was observed in sensorimotor performance. Females demonstrated increased circulating levels of LPS ($p=0.0023$) and the pro-inflammatory factor, RANTES, ($p=0.0037$). Additionally, there was an interaction effect of sex X housing on the pro-inflammatory factor MIP-1α. **Conclusions:** Increased LPS after stroke suggests greater gut permeability, which, coupled with elevated cytokine expression, could impact blood brain barrier permeability, resulting in more severe chronic stroke outcomes in females. Our data indicate a sex-specific effect of SI on the gut-immune response to stroke.

Disclosures: M.E. Zardeneta: None. **T. Branyan:** None. **F. Sohrabji:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.04/Q1

Topic: C.09.Stroke

Support: IK2 RX002837

Title: Coherence of corticospinal tract microstructure in chronic stroke survivors

Authors: *S. BIKMAL[1,2], F. LIU[1,2], C.-H. MOON[1,2], J. L. COLLINGER[1,2], G. F. WITTENBERG[1,2], M. A. URBIN[1,2];
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Abstract: Corticospinal tract (CST) microstructure is a predictor of motor function in chronic stroke survivors. CST anisotropy and diffusivity are typically quantified from discrete regions of interest along the length of the tract, but this approach is not always feasible at the chronic stage when extensive brain atrophy has occurred. Extracting measurements from a greater portion of the CST in areas of surviving white matter is subject to heterogeneity in the location/extent of damage; confounds, such as fiber crossings, can also bias estimates in the absence of any white matter abnormality. Here, we aimed to characterize asymmetries in white matter microstructure along the length of the residual CST. Stroke survivors (n=16, 8 females, 61.2±9.1 years) with longstanding hand impairment (99.1±78.2 months) and neurologically-intact controls (n=20, 10 females, 60.3±10.2 years) underwent 3T MRI (Siemens, Prisma-fit). Diffusion spectrum imaging (DSI) data were acquired (2D spin-echo EPI; TR/TE= 2490/99.2ms, voxel=2 mm^3, diffusion direction=258, max b-value=4000 s/mm^2, acquisition time=11min) and preprocessed using FSL (http://www.fmrib.ox.ac.uk/fsl). A deterministic fiber tracking algorithm (angular threshold=60°, step size=1 mm) was used to reconstruct CSTs from primary motor cortex to brainstem. DSI metrics were computed at each slice and included voxel- and population-based metrics of fractional (FA) and quantified (QA) anisotropy, respectively, as well as mean (MD), axial (AD), and radial (RD) diffusivities. Metrics were expressed as ratios in controls (non-dominant/dominant CST) and stroke survivors (lesioned/intact CST). Spearman correlations revealed reduced coherence in stroke survivors (ρ=0.50-0.64) relative to controls (ρ=0.83-0.92) for all metrics. Using distributions from controls, metric ratios > 3 standard deviations below (FA and QA) and above (MD, AD, and RD) the sample mean were set as the threshold for identifying abnormal asymmetries in the CST segment overlapping with the infarct volume, as well as segments rostral and caudal to this overlap. The infarct segment contained the greatest percentage of abnormal asymmetries (FA=11.3%, QA=9.7%, MD=17.6%, AD=12.5%, and RD=17.9%) with progressively fewer in caudal (FA=4.1%, QA=3.5%, MD=7.2%, AD=4.2%, and RD=8.8%) and rostral (FA=1.2%, QA=0.9%, MD=1.8%, AD=1.6%, and RD=1.7%) segments, respectively. These results show a disruption in CST microstructure coherence that is most prevalent in the portion of the CST overlapping with the infarct. Further work is needed to determine whether and how microstructural asymmetries in each segment of the residual CST relate to motor function.

Disclosures: S. Bikmal: None. **F. Liu:** None. **C. Moon:** None. **J.L. Collinger:** None. **G.F. Wittenberg:** None. **M.A. Urbin:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.05/Q2

Topic: C.09.Stroke

Support: NIH Grant R41NS124450
NIH Grant RF1NS131110

Title: Localizing microglia, B-cell, and T-cell populations to 30-day post stroke injury using immunohistochemistry and magnetic resonance imaging in a mouse model of ischemic stroke and reperfusion.

Authors: D. C. DICKSON, D. P. MURPHY, A. N. FATEMA, T. P. TROUARD, ***H. MORRISON**;
Univ. of Arizona, Tucson, AZ

Abstract: Due to the lipid rich nature of the brain, post-stroke healing occurs differently than other organs/systems. While a large portion of stroke literature examines outcomes at acute time-periods, less is known regarding brain wound healing and the immune response at chronic timepoints in stroke rodent models. Using functional activity measures, magnetic resonance imaging (MRI), assays of serum neurofilament light (NFL) concentrations, and fluorescence immunohistochemistry (IHC), we describe post stroke brain injury outcomes, immune cell responses and infiltrates in the healing brain of male (n = 12) and female mice (n = 7; 15 weeks old) at 30 days post stroke (DPS). Functional activity was assessed 1 week prior to occlusion of the middle cerebral artery (45 min.) with additional assessments at 2 and 30 DPS; MRI assessment occurred at 2 and 30 DPS. Brain tissue and serum were collected at 30 DPS. Coronal brain sections, 5-7/mouse spanning bregma 1.5 to -4.0, were used for IHC to quantify: microglia process length/cell and endpoints/cell and the %area of phagocytic receptor CD68 in ipsilateral and contralateral regions as well as B-cell/CD220 and T-cell/CR45e positive areas in the ipsilateral hemisphere. Survival assessment shows that 86% of female mice (n= 6) survived to 2 and then 30 DPS whereas 42% of male mice (n=5) survived to 2 DPS and 33% (n=4) survived to 30 DPS. Sex differences in 30-day survival was significant ($X^2_{(1, 19)} = 4.46$, $p = 0.03$) and no sex differences were observed in infarct volume among surviving mice at either timepoint (2 DPS: $p = 0.15$, 30 DPS: $p = 0.37$). Principal component analysis was carried out to analyze the multiple parameters comprising functional activity from activity chambers. PC1 was significantly increased in male but not female mice at 2 DPS and PC1 was increased in both male and female mice after 30 DPS ($F_{(2, 38)} = 25.41$, $p < 0.0001$; sex: $F_{(1, 38)} = 0.54$, $p = 0.47$; interaction $F_{(2, 38)} = 6.45$, $p = 0.004$). PC2 was not significantly different according to sex or time post-stroke. NFL serum concentrations persist at 30 DPS and are different according to sex ($p = 0.04$). A significant and non-linear relationship exists between infarct volume and NFL concentrations (male: $r = 0.99$; female: $r = 0.98$). While B-cells are abundant in the residual injury, T-cells are scarce. Microglia responses 30 DPS (morphology and CD68) are present only adjacent to the region of residual brain injury versus distal region ($p > 0.05$) and not influenced by sex. Combined, these data illustrate a continued and rigorous wound healing response at 30 DPS; the outcomes of this response, extending beyond injury size, may be different according to sex and important to treatment paradigms.

Disclosures: D.C. Dickson: None. **D.P. Murphy:** None. **A.N. Fatema:** None. **T.P. Trouard:** A. Employment/Salary (full or part-time):; University of Arizona. **H. Morrison:** A. Employment/Salary (full or part-time):; University of Arizona. 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.; Co-PI on NIH funded STTR drug study.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.06/Q3

Topic: C.09.Stroke

Support: NIH/NINDS grant RF1NS117486

Title: [^{18}F]-FDG-PET/CT analysis of the glucose metabolism in a mouse model of Dominant Arteriopathy with Subcortical infarcts & Leukoencephalopathy

Authors: *L. LETICA, L. LJUNGQVIST BRINSON, S. K. PELL, S. H. CHOI, D. SZCZUPAK, J. E. PARK, D. J. SCHAEFFER, A. C. SILVA;
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Abstract: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the most common inherited small-vessel disease, is associated with mutations in the Notch3 gene that encodes a cell surface receptor on vascular smooth muscle cells (VSMCs) and pericytes. While the cerebral blood flow impairments in CADASIL have been well documented, a possible association between Notch3 mutations and brain glucose metabolism remains unclear. With the hypothesis that brain glucose metabolism is disrupted in CADASIL, we used 2-deoxy-2-[^{18}F]-fluoro-D-glucose ([^{18}F]-FDG)-PET/CT and gene and protein expression of glucose transporters via Western blot analysis to investigate brain glucose uptake in the Notch3^{C456R} knock-in mouse model of CADASIL. ^{18}F-FDG was delivered to awake mice via a tail vein injection, with an average dose of 18.5 mBq. PET and CT acquisitions were completed after a 30-minute ^{18}F-FDG circulation period using a Bruker Si78 instrument. Static datasets were analyzed for standard uptake values relative to the brainstem (SUV_r) and corrected for glucose levels (SUV_{glc}). Animal body weight did not differ between genotypes and across age groups. Blood glucose levels measured before ligand injection show that, on average, Notch3C456R mice have lower levels than age-matched wild-type (WT) mice. Whole brain representative images of average SUV_r values show an age-dependent increase in ^{18}F-FDG uptake across 6, 15, and 20-month Notch3^{C456R} mice. 15-month-old Notch3^{C456R} mice exhibited significantly lower metabolism in the striatum, cortex, hippocampus, thalamus, cerebellum, hypothalamus, central gray matter, olfactory bulb, midbrain, and superior & inferior colliculi compared to age-matched WT mice. Notch3^{C456R} mice show an age-dependent increase in Notch3 extracellular domain protein (N3ECD). Western Blot data analysis of 6- and 20-month-old samples indicates that the aged Notch3^{C456R} cohort has lower levels of GLUT-1, a glucose transporter protein, compared to 6-month Notch3^{C456R} mice and 20-month-old WT controls. Decreases in GLUT-1 transporter protein and glucose uptake in aged Notch3 ^{C456R} mice coupled with an age-dependent increase of N3ECD provide compelling evidence of glucose metabolism disruption in the CADASIL mouse model. These results show a strong association between Notch3 mutations and decreased brain glucose metabolism.
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Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

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Program #/Poster #: PSTR078.07/Q4

Topic: C.09.Stroke

Support: NIH CTSA UL1 award 2UL1TR002378

Title: Delineating the human direct and indirect motor descending pathways using high-resolution tractography with diffusion imaging

Authors: *D. RAI[1], A. NOORANI[2], T. D. VERSTYNEN[3], J. XU[2];
[1]Kinesiology, [2]Univ. of Georgia, Athens, GA; [3]Psychology, Univ. California, Berkeley, CA

Abstract: Dexterous hands are essential in our daily activities. Previous research has established that fine finger control and hand strength are supported by separate descending pathways, namely, the corticospinal (CST) and reticulospinal tracts (RST). Recent non-human primate research suggests that after lesion of the direct, corticomotoneuronal projections within the CST (dCST), the indirect connections within the CST (iCST), specifically the propriospinal (PN) pathway, also contributes to the recovery of hand dexterity (Isa, 2019). Delineating these descending pathways will be informative to functional recovery after neurological insult. Comparative fiber tracking studies across species suggests that the majority of the dCST in humans originates from M1 (Brodmann's area BA4) (Lassek & Rasmussen, 1940) and the PN pathway mainly originate from ventral premotor cortex (PMv) (BA6) (Pierrot-Deseilligny, E. & Burke, 2005). Here, we investigated the feasibility of using a recent ultra-high-resolution whole-brain atlas from the HCP data to separate dCST, iCST, and RST in healthy and stroke populations. Diffusion MR images (dMRI) were collected from healthy older adults (N=8) and individuals with stroke (N=2) on a 3T GE scanner (Discovery MR750). We used readout-segmented echo-planar imaging in conjunction with parallel imaging (Heidemann et al., 2010) and a multi-shell diffusion spectrum imaging sequence. The dMRI images were reconstructed to the MNI space using q-space diffeomorphic at an output resolution of 1 mm isotropic (Yeh et al., 2010). Fibers were first restricted by BA4, BA6 and brainstem ROIs and then tranced starting from the internal capsule (IC) and between the cortex and cerebral peduncle (CP) (Verstynen et al, 2011). For the RST pathways we used seed in the posterior segment of the brainstem, behind and dorsal to the pons, following previously identified locations in voxel-space (Karbasforoushan et al., 2019).To assess tract integrity of different pathways affected by the lesion, we first generated ROI masks of the approximate dCST, iCST and RST pathways in the HCP atlas. The average Quantitative anisotropic (QA) values of the descending fibers identified in these masks were then extracted per participant and compared between patients and controls. Our results showed that the QA values of two-stroke patients' lesioned side (Mean ± SD: dCST:

0.22 ± 0.008 ; iCST: 0.23 ±0.016; RST: 0.23 ± 0.012) were at the lower end of the QA distributions of the healthy participants (dCST: 0.26 ± 0.015; iCST: 0.24 ± 0.018; RST: 0.27 ± 0.024). These results indicate that our method can effectively assess fiber integrity within the direct and indirect CST and RST.

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Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

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Program #/Poster #: PSTR078.08/Q5

Topic: C.09.Stroke

Support: 1R03 NS128459-01

Title: 2p-liasn enables functional in vivo single cell tracking of therapeutic cells for stroke treatment

Authors: *J. WANG[1], P. WALCZAK[3], Y. LIANG[2];
[1]Diagnos. Radiology and Nuclear Med., [2]Univ. of Maryland Sch. of Med., Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Radiology, Johns Hopkins Univ., Baltimore, MD

Abstract: Replacement cell therapy for stroke using neural stem cells or progenitor cells has been extensively pursued for several decades. However, a major obstacle in this field is the limited integration of donor cells with the host neural circuits. Methodologically, there is a strong need to elucidate the post-transplantation behavior of grafted cells in real-time, with high spatial and temporal resolution, through intravital imaging. Unfortunately, most studies rely on static histology as the readout, which fails to provide dynamic insights into the behavior of these cells. To address this gap, we have developed a novel multiplexed cell labeling method called 2pLIASN (Location, Identify, Activity of Self and Neighbors under 2-photon microscopy), which allows for single-cell tracking of donor cells and functional assessment of communication between donor and host cells in live animals. The LIASN system consists of two components: the first involves labeling cells with genetically encoded calcium indicators, specifically green (GCaMP) for donor cells and red (jRGECO1a) for host cells. The second component assigns an identity to each cell using a modified version of the Brainbow labeling technique, employing a distinct set of fluorescent proteins (RBI, mCherry as R, TagBFP2 as B, and iRFP682 as I). Spatial unmixing is achieved by targeting GCaMP to nuclei and RBI fluorophores to the cytosol of donor cells. By transducing cells with a lentiviral mixture of functional RBI labeling vectors (RBI-H2B-GCaMP6s), donor cells exhibit a variety of colors in the cytosol and GCaMP in the nuclei, enabling reliable cell tracking and functional imaging. Meanwhile, host neurons are labeled with jRGECO1a using transgenic mice. LIASN represents a significant improvement over our previously published cell positioning system for cell tracking and constitutes a valuable addition to the long-term intravital single-cell tracking toolkit. We have demonstrated the

efficacy of LIASN by applying it to stem cell therapy for stroke, showcasing its immense potential in enhancing our comprehension of donor-host interactions and providing crucial insights for the development of novel strategies in cell replacement therapy for stroke.

Disclosures: **J. Wang:** None. **P. Walczak:** None. **Y. Liang:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.09/Web Only

Topic: C.09.Stroke

Title: A retrospective cohort study of COVID-19 positive patients with stroke at a comprehensive stroke center: Preliminary results from 70 patients

Authors: C. BETTS[1], Z. AHLFINGER[1], L. AYARI[2], *B. KIRMANI[3,4];
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Abstract: Rationale: COVID-19 is no longer a global health emergency, but it still poses a significant health concern due to its widespread nature and potential extrapulmonary manifestations. The aim of this project is to review the CHI St. Joseph Health Bryan Regional Hospital Comprehensive Stroke Center experience with COVID-19-positive patients who were diagnosed with stroke in regards to risk factors, hospital course, prognosis, and outcome.Methods: This is a retrospective study to review the hospital records of COVID-19-positive patients who were diagnosed with stroke within 2 months of a COVID-19 diagnosis from January 1, 2020, to February 28, 2023, at the comprehensive stroke center. Subject data were acquired from electronic medical records. Approval of this retrospective analysis was given by our central CHI Health Institutional Review Board. Results: In this study, we report our preliminary retrospectively analyzed data on 70 patients who were diagnosed with stroke within 2 months of COVID-19 infection. The Median age is 69. There were 39 (55.7%) females and 31 (44.3%) males. 40 were white/caucasian (57.1%), 15 were african american (21.4%), and 15 were Latino (21.4%). 46 (65.7%) ischemic strokes, 20 (28.6%) transient ischemic attacks, and 4 (5.7%) hemorrhagic strokes were diagnosed. Of the ischemic strokes, 29 (63%) presented with neurological symptoms, and 13 (28.3%) presented with respiratory symptoms, and had a stroke in the subsequent hospitalization. 19 (41.3%) patients had occlusion of the middle cerebral artery (MCA) or its branches, 8 (17.4%) had bilateral occlusions, and 7 (15.2%) had lacunar infarcts. Of the ischemic strokes that occurred after the first approval of a COVID-19 vaccine, vaccination status was unknown in 20 (54.1%), confirmed in 9 (24.3%), and unvaccinated in 8 (21.6%). The patients had a median of 2.5 vascular comorbidities, the most common of which were hypertension, dyslipidemia, and diabetes mellitus. The median National Institutes of Health Stroke Scale is 6 at admission with a median change of -1.5. The median length of stay was 8.5

days. The median modified Rankin Scale is 4 at discharge. 15 (32.6%) patients were discharged home, 12 (26.1%) to inpatient rehabilitation, 6 (13%) to skilled nursing facilities, 2 (4.3%) to hospice, and 10 (21.7%) expired. Conclusions: Our preliminary data suggest that stroke is seen in patients hospitalized with COVID-19 illness, but more commonly occurs as the presenting symptom for hospital admission. Most strokes were ischemic involving the MCA territory, and were debilitating to patients. Older patients and those with vascular risk factors may be at risk for stroke after COVID-19 infection.

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Poster

PSTR078. Assessment and Imaging of Stroke

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Program #/Poster #: PSTR078.10/Q6

Topic: C.09.Stroke

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KU Leuven C14/18/099-STYMULATE-STROKE
FWO MEDI-RESCU2-AKUL/17/049, G091719N, and 1197818N
VIB Tech-Watch fUSI-MICE
NERF TechDev fund 3D-fUSI project

Title: Functional ultrasound imaging of stroke in awake rats

Authors: *C. BRUNNER[1], G. MONTALDO[2], A. URBAN[2];
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Abstract: Anesthesia is a major confounding factor in preclinical stroke research as stroke rarely occurs in sedated patients. Moreover, anesthesia affects both brain functions and the stroke outcome acting as neurotoxic or protective agent. So far, no approaches were well suited to induce stroke while imaging hemodynamics along with simultaneous large-scale recording of brain functions in awake animals. For this reason, the first critical hours following the stroke insult and associated functional alteration remain poorly understood. Here, we present a strategy to investigate both stroke hemodynamics and stroke-induced functional alterations without the confounding effect of anesthesia, i.e., under awake condition. Functional ultrasound (fUS) imaging was used to continuously monitor variations in cerebral blood volume (CBV) in +65 brain regions/hemisphere for up to 3hrs after stroke onset. The focal cortical ischemia was induced using a chemo-thrombotic agent suited for permanent middle cerebral artery occlusion in awake rats, and followed by ipsi- and contralesional whiskers stimulation to investigate on the dynamic of the thalamo-cortical functions. Early (0-3hrs) and delayed (day 5) fUS recording enabled to characterize the features of the ischemia (location, CBV loss), spreading depolarizations (occurrence, amplitude) and functional alteration of the somatosensory thalamo-cortical circuits. Post-stroke thalamo-cortical functions were affected not only early after the

stroke onset but were also altered secondarly and remotely from the initial insult. Overall, our procedure enables early, continuous, and chronic evaluations of hemodynamics and brain functions which, combined to stroke or other pathologies, aims to better understand physiopathologies toward the development of clinically relevant therapeutic strategies.

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Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR078.11/Q7

Topic: C.09.Stroke

Support: NIH Grant NS097620
NIH Grant NS128469
NSF Grant 2048231
AHA 23PRE1018175
AHA 897265
AHA 847486
Cedars-Sinai

Title: Non-rapid eye movement sleep features in post-stroke human electroencephalogram

Authors: R. RANGWANI[1], B. SIMPSON[2], A. ABBASI[2], J. M. CHUNG[2], C. M. REED[2], ***T. GULATI**[3];
[1]UCLA, Los Angeles, CA; [2]Cedars-Sinai, Los Angeles, CA; [3]Cedars-Sinai/ UCLA, Los Angeles, CA

Abstract: Sleep is known to promote recovery post-stroke. However, there is a paucity of data profiling nested sleep oscillations post-stroke in the human brain to identify biomarkers of recovery. Recent rodent work showed that resurgence of physiologic spindles (10-16Hz) coupled (‘nested’) to sleep slow oscillations (SOs, < 1Hz) and concomitant decrease in pathological delta (δ, 1-4Hz) waves is associated with sustained motor performance gains during stroke recovery. This work also showed that post-injury sleep could be pushed toward a physiological state via a pharmacological reduction of tonic γ-aminobutyric acid (GABA). We evaluated non-rapid eye movement (NREM) sleep oscillations (namely, SOs, spindles and δ waves, and their nesting) in the post-stroke human brain and compared them with these recent rodent findings. We analyzed NREM-marked electroencephalography (EEG) data in human stroke patients who were hospitalized for stroke and received EEG monitoring as part of their clinical workup. Electrodes were classified as ‘stroke’ (immediate peri-infarct areas) or ‘contralateral’ (unaffected hemisphere). Using linear mixed models, we found significant random effects of patients and concurrent pharmacologic drugs during EEG data capture. Like recent rodent data, we found that δ waves increased in peri-infarct electrodes versus contralateral electrodes, for most patients

studied. This trend was only different in a stroke patient on continuous propofol and scheduled dexamethasone (δ waves density was high in both hemispheres). SO density followed the trend seen in δ wave density. For SO-nested spindles, the hallmarks of reparative sleep, we did not find a significant difference between stroke and contralateral electrodes acutely after stroke. However, δ wave-nested spindles, that are harmful to recovery related plasticity, were high in groups who received propofol or levetiracetam. These findings suggest that, acutely post-stroke, pathological δ waves increase in the human brain and that spindle density may be impacted by drugs that modulate excitatory/inhibitory neural transmission. Further, we found that drugs that increase inhibitory transmission or curb excitation, promote pathological δ wave-nested spindles. Our results indicate that factoring in pharmacologic drugs may be important when targeting sleep modulation for neurorehabilitation.

Disclosures: **R. Rangwani:** None. **B. Simpson:** None. **A. Abbasi:** None. **J.M. Chung:** None. **C.M. Reed:** None. **T. Gulati:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.12/Q8

Topic: C.09.Stroke

Title: Lesion symptom mapping of behavioral dysregulation

Authors: *A. THOMAS[1,2], J. BRUSS[1,3,4], D. TRANEL[1,2,5], A. BOES[1,3,4,5,6];
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Abstract: The ability to regulate one's behavior is important for adaptive functioning and maintaining social relationships. Behavior dysregulation consists of acts that generally oppose social norms and may be harmful to others. Following a brain lesion, individuals can acquire disturbances in regulating their behavior. Such disturbances are characterized by impairments in impulse control, decision making, and social conduct. This could include aggressive behavior, substance abuse, rule breaking, and excitement seeking. Several brain regions and networks have been correlated with performance on tasks requiring behavior regulation, yet the brain regions most causally implicated for real-world behavior regulation are not fully understood. The current project leverages a large cohort of individuals with focal brain lesions to evaluate which brain regions, when damaged, are associated with behavioral dysregulation. Participants included 226 patients (47% women, mean age 47.1 years) from the Iowa Neurological Patient Registry. Participants all had a focal, acquired brain lesion 3 months or more prior to assessment. Behavior was measured using the Minnesota Multiphasic Personality Inventory II, Restructured Form (MMPI-2-RF), a widely used measure of personality and psychopathology. The Behavioral Dysfunction scale of the MMPI-2-RF is comprised of 71 items and provides an overall gauge of an individual's tendency to engage in under-controlled behaviors. It includes several subscales

such as substance use, impulsivity, and aggression. Each brain lesion was manually traced and transformed to a common template brain (MNI152). We used multivariate lesion-symptom mapping with sparse canonical correlation analysis (LESYMAP) to investigate the neuroanatomical correlates of behavioral dysregulation. Lesions of the left dorsomedial prefrontal cortex (dmPFC) and the anterior cingulate (ACC) were associated with higher levels of behavioral dysregulation ($r = 0.136$, $p = .041$). These findings support prior work that has attributed these brain regions with flexible behavioral control, decision making, and performance monitoring. Understanding the anatomical regions most critical for behavior regulation could help identify patients at risk for behavioral dysregulation after a brain injury. This line of work may also be important for understanding the pathophysiology of brain disorders characterized by behavioral dysregulation in individuals without macroscopic lesions, and even inform potential therapeutic targets for neuromodulation.

Disclosures: **A. Thomas:** None. **J. Bruss:** None. **D. Tranel:** None. **A. Boes:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.13/R1

Topic: C.09.Stroke

Title: Correlating neuroanatomical lesions to impaired consciousness in patients with acute ischemic stroke

Authors: *Z. ZHANG[1], M. WHITE[1], J. A. KIM[1], V. M. TORRES-LOPEZ[1], D. S. JIN[1], A. KHALAF[1], K. N. SHETH[2], H. BLUMENFELD[3];
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Abstract: Acute ischemic stroke (AIS) can cause severe impaired consciousness including coma, leading to poor clinical outcomes and death. AIS may manifest infarction in a variety of neuroanatomical locations in the brain, providing an opportunity to investigate brain anatomy related to coma. Modern neuroimaging methods have the potential to identify neuropathological correlates implicated in coma-related stroke. The purpose of this study is to explore the neuroanatomical correlates associated with coma by comparing AIS patients with coma with control AIS patients without coma. The source population is AIS patients admitted to a single tertiary care referral center. Patients who underwent MRI scans within 7 days from clinical brain ischemic stroke and coma onset are included. MRI scans are required to include diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), T1-weighted and T2-weighted images. Identifying patients with or without coma is based on Glasgow Coma Scale and clinical chart review, such as reviewing patient's medical chronology including the onset and offset of symptoms and coma, whether thrombectomy or intravenous thrombolysis were administered, and the outcome of thrombectomy or intravenous thrombolysis if applicable. Patients with

intermediate levels of impaired consciousness, or with causes of impaired consciousness not attributed to AIS (e.g., toxic-metabolic dysfunction, head trauma, seizures, medications, etc.) are excluded. A total of 914 patients with AIS met key inclusion criteria. 13 patients were identified as having coma and experienced coma duration varying from 1.75 hours to 6 days. Based on visualization of DWI and ADC maps, patients with coma showed lesions in bilateral or unilateral brainstem, cerebellum, thalamus, and widespread areas of cerebral cortex. Lesion segmentation of DWI images using Horos software and quantitative analyses (support vector regression lesion-symptom mapping) to determine lesion locations associated coma are ongoing. We are expecting to reveal potential associations between coma and damage to subregions in the brainstem or other subcortical structures (e.g., hypothalamus, thalamus), and between coma and damage to specific regions of bilateral parietal and/or frontal cortex or other cortical regions. We hope that findings from this study can help accurately identify the signs and symptoms to promote early and comprehensive management and treatment for patients with AIS and shed light on critical cortical and subcortical brain regions necessary for normal consciousness.

Disclosures: Z. Zhang: None. **M. White:** None. **J.A. Kim:** None. **V.M. Torres-Lopez:** None. **D.S. Jin:** None. **A. Khalaf:** None. **K.N. Sheth:** None. **H. Blumenfeld:** None.

Poster

PSTR078. Assessment and Imaging of Stroke

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.14/R2

Topic: C.09.Stroke

Support: COBRE in Stroke Recovery
College of Charleston Undergraduate Research and Creative Activities Office (URCA)-MAYS Grant

Title: Serum and Neuronally Derived Exosome BDNF Levels in Stroke Patients and its Relationship with Metabolic Outcome Measures

Authors: *M. SADDOW[1], S.-K. SIMS[1], L. S. WATSON[2], W. INVESTIGATORS[2], C. S. ROBINSON[2];
[1]Biol., Col. of Charleston, Charleston, SC; [2]Med. Univ. of South Carolina, Charleston, SC

Abstract: ***Introduction:*** Low circulating levels of brain derived neurotrophic factor (BDNF) has been associated with poor long term functional outcomes after ischemic stroke. BDNF has been also associated with abnormal levels of triglycerides, cholesterol, and hemoglobin A1C, which often precedes and exacerbates complications after stroke onset. Given the links between BDNF and post-stroke recovery, there is a need to develop additional methodologies that accurately reflect BDNF levels in the brain. As BDNF levels in serum and neuronally derived exosomes (NDE) are indicative of greater post-stroke recovery, these studies aimed to explore the correlations between metabolic factors and BDNF. This study focuses on the correlational links

between BDNF and adverse metabolic outcomes in human stroke patients. ***Materials and methods***: This project was a part of the American Heart Association/American Stroke Association Strategically Funded Research Network Wide Spectrum Investigation of Stroke Outcome Disparities on Multiple Levels (WISSDOM) study. 60 Patients between the ages of 30-75, without a prior history of stroke, were randomly selected. Within this study, all subjects self-reported as not currently pregnant. Patients did not have a history of terminal illness with life expectancy of < 1 year, history of dementia, or a diagnosis of substance abuse. A subset of 30 patient serum samples were used in analysis for enzyme-linked immunosorbent assay (ELISA) analysis for both mature BDNF and proBDNF in serum and NDE. The isolation of extracellular vesicles (EVs) was processed from aliquots (0.5 ml) of plasma from randomly selected patients. Modified Rankin Scores (mRS) and Stroke Impact Scale (SIS) outcome measures were also obtained from these patients at baseline, 3, 6, and 12 months post-stroke. Correlations were also performed between serum and exosome BDNF levels, metabolic measures (triglycerides, hemoglobin A1C, and cholesterol) and functional outcomes. ***Results and Conclusions:*** Serum analysis revealed that mature BDNF steadily increased at 3- and 12-months post-stroke compared to baseline while proBDNF serum levels decreased at each post-stroke timepoint indicating a possible predictive relationship between BDNF and stroke recovery. Mature BDNF serum levels were also positively correlated with overall recovery on the mRS assessment. Additional analysis also reveals that higher proBDNF serum and NDE levels correlate with higher A1C, cholesterol and triglyceride levels. Future directions will be to analyze the BDNF produced in glial derived exosomes as a possible indicator of post-stroke recovery.

Disclosures: M. Saddow: None. **S. Sims:** None. **L.S. Watson:** None. **W. Investigators:** None. **C.S. Robinson:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

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Program #/Poster #: PSTR079.01/R3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 5R01NS064004
NYSDOH SCIRB C37716GG

Title: Electrical neuromodulation of the primary motor cortex identifies biomarkers for corticospinal tract axon growth state and synaptic plasticity

Authors: *N. ZAREEN[1], H. YUNG[2], H. ALEXANDER[1], J. H. MARTIN[1];
[1]Molecular, Cellular, Biomed., [2]Sophie Davis, CUNY Sch. of Med., New York, NY

Abstract: Long-term motor cortex (MCX) electrical stimulation promotes CST sprouting to repair the corticospinal tract (CST) after injury. We have used long-term (LT, 10 daily sessions) multi-pulse stimulation (MPS) and intermittent theta burst stimulation (iTBS) to repair the CST

after pyramidotomy and SCI, respectively. MCX MPS increases mTOR and Jak/Stat signaling in CST neurons, which are necessary for CST sprouting and synapse formation, respectively. Importantly, long-term MPS deactivates PTEN by increasing its phosphorylation, without suppressing protein expression. MPS and iTBS differ from each other in stimulation pattern, duration, and possibly capacity to induce plasticity and CST outgrowth. We, therefore, asked how their molecular underpinnings differ. We also examined how stimulation duration (short-term [ST; 1 session] versus LT) affected molecular signaling. Answering these questions is important for developing therapeutic neuromodulation protocols. We found that iTBS, not MPS, promotes CST sprouting with ST stimulation. Whereas iTBS increased mTOR and decreased PTEN signaling, MPS only increased mTOR. LT stimulation converted MPS to be effective in promoting CST sprouting. This is associated with both increased mTOR and decreased PTEN signaling. LT iTBS also produced CST sprouting and increased mTOR and decreased PTEN signaling. These findings show that combined increased mTOR and decreased PTEN signaling accompany CST outgrowth induced by neuromodulation. We next tested plasticity of MCX-evoked muscle response (MEP) recruitment. ST MPS and iTBS both produced transient MEP plasticity. LT MPS also produced transient MEP plasticity. However, LT iTBS produced durable MEP plasticity, persisting for 20+ days post-stimulation. Jak/Stat signaling was activated for all conditions that produced MEP enhancement, whether transient or persistent. After cervical SCI, LT MPS produced mTOR activation and PTEN deactivation, but LT iTBS additionally produced increased Jak/Stat signaling. Our findings suggest that the combined increase in mTOR and decrease in PTEN is a biomarker for activity-dependent CST sprouting and that increased Jak/Stat signaling is a biomarker of MEP plasticity. LT iTBS is optimal for SCI, since it activates both growth and MEP plasticity markers.

Disclosures: **N. Zareen:** None. **H. Yung:** None. **H. Alexander:** None. **J.H. Martin:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.02/R4

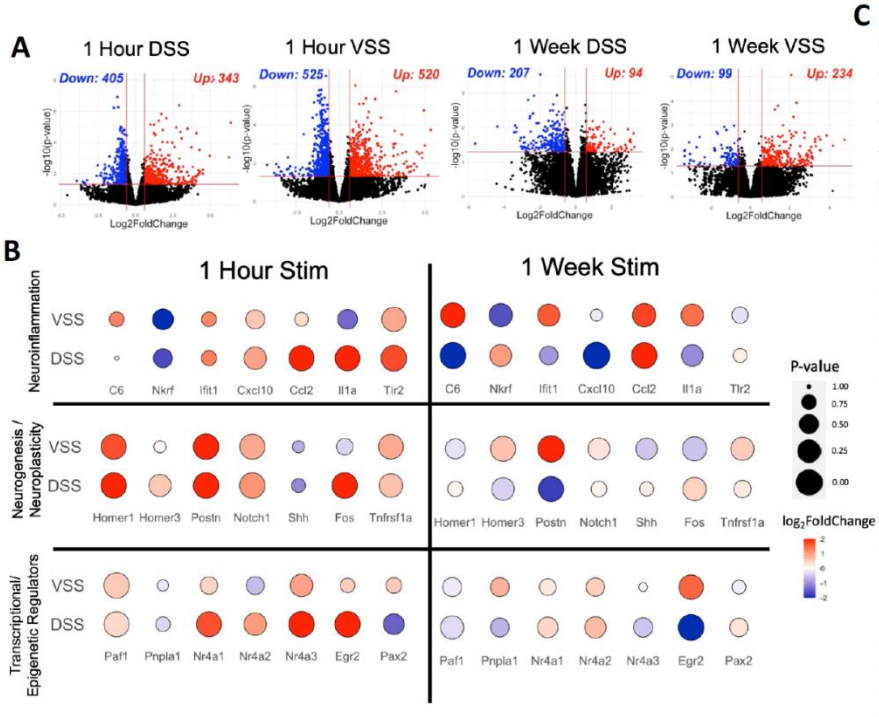
Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings For Life Foundation Grant WFL-US-06/22-268
Craig H. Neilsen Foundation Grant 599274

Title: Neuromodulation Drives Microglial/Inflammatory Neuroprotective Phenotype in a Rat Cervical Spinal Cord Injury Model

Authors: *J. A. MEJIA[1], M. HOGAN[2], Y.-L. WENG[2], P. J. HORNER[2];
[1]Physiology, Biophysics, and Systems Biol., Weill Cornell Med. Col., Houston, TX; [2]Houston Methodist Res. Inst., Houston, TX

Abstract: ABSTRACT Microglia play an important role in maintaining and repairing the central nervous system (CNS) after traumatic injuries. Recent work has demonstrated that the suppression of microglia during spinal cord injury (SCI) led to a decrease in neuroregeneration, less gene diversity in the remaining cell populations, and overall worsening of functional outcomes. Moreover, modulation of microglia phenotype through genetic and pharmaceutical models shows promising results in understanding the role of microglia during SCI. There is little work characterizing microglia phenotype *in vivo* during neuromodulation/electrical stimulation. Neuromodulation is one of the few clinically-relevant treatments for functional recovery after SCI but the exact mechanism(s) that takes place during this treatment are under-explored. This presentation shows preliminary data that demonstrate phenotypic changes in microglia during cervical SCI and electrical stimulation and how that may lead to functional improvements. In our *Rattus Norvegicus* model, a cervical spinal cord contusion injury at C4 was induced with a constant displacement impactor, and epidural electrodes were implanted at C6 one week post-injury. Electrical stimulation occurred for one hour followed by immediate isolation of the stimulated spinal segment. A sham device was used for the control group. Functional forelimb reaching task (FRT) analysis demonstrated an improvement in the volitional movement of upper limbs post-neuromodulation compared to a non-stimulated control by 7 weeks post-injury. Through bulk RNAseq, we observe over 700 significant differential gene changes in the presence of neuromodulation. Gene Ontology revealed a high enrichment of genes in the neuroinflammatory pathways. This suggests a critical role of microglia/immune cells in the CNS that can be altered by neuromodulation. This research was funded in part by a grant from the Wings for Life Foundation.



C

DSS 1 Hour Upregulated Pathways

Process	GO: ID	p-adj
response to mechanical stimulus	GO:0009612	4.05E-05
cellular response to interleukin-1	GO:0071347	1.81E-04
response to chemokine	GO:1990868	2.15E-04
cellular response to chemokine	GO:1990869	2.15E-04
positive regulation of leukocyte migration	GO:0002687	2.46E-04

VSS 1 Hour Upregulated Pathways

Process	GO: ID	p-adj
wound healing	GO:0042060	3.41E-04
defense response to virus	GO:0051607	5.74E-04
defense response to symbiont	GO:0140546	5.74E-04
response to virus	GO:0009615	1.49E-03
regulation of response to biotic stimulus	GO:0002831	1.49E-03

DSS 1 Week Upregulated Pathways

Process	GO: ID	p-adj
neutral lipid biosynthetic process	GO:0046460	0.162
acylglycerol biosynthetic process	GO:0046463	0.162
inorganic anion transmembrane transport	GO:0098661	0.162
excitatory postsynaptic potential	GO:0060079	0.162
chemical synaptic transmission, postsynaptic	GO:0099565	0.162

VSS 1 Week Upregulated Pathways

Process	GO: ID	p-adj
collagen fibril organization	GO:0030199	3.94E-03
cell-substrate adhesion	GO:0031589	3.94E-03
connective tissue development	GO:0061448	3.94E-03
regulation of vasculature development	GO:1901342	3.94E-03
extracellular matrix organization	GO:0030198	3.94E-03

Figure 4. Ventral and Dorsal neurostimulation have distinct expression patterns in acute and sub-acute SCI. Differential gene lists were generated with an injured animal with a sham electrode as the control. **(A)** Volcano plots of DSS and VSS at 1 hour and 1 week of stimulation show that neurostimulation causes an initial increase in DEG's that seems to plateau/stabilize by 1 week and that VSS stimulated more distinct genes compared to DSS. **(B)** Examples of distinct and conserved gene changes clustered by function; Neuroinflammation, Neurogenesis/Neuroplasticity, and Transcriptional/Epigenetic Regulators. These data demonstrate that immediate gene expression changes in response to neurostimulation can vary highly to the gene expression at 1 week of daily stimulation depending on the modality of stimulation (VSS or DSS). **(C)** Top 5 upregulated gene ontology terms (GO) for VSS and DSS at 1 hour and 1 week of stimulation. At 1 hour of stimulation, upregulated GO pathways in both VSS and DSS are having to do with inflammatory response and healing. However, by 1 week DSS has no more significant upregulated GO pathways while VSS seems to have shifted to more of an ECM remodeling phenotype. This suggests that ventral stimulation has a longer lasting effect that would possibly be harnessed either in conjunction to DSS or a possible replacement therapy.

Disclosures: **J.A. Mejia:** None. **M. Hogan:** None. **Y. Weng:** None. **P.J. Horner:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.03/R5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01-NS115025-01A1
DP1-AT011991
DMR-1419807
EEC-1028725
R21-AT010818
DP2-MH122402
R01-DK131112

Title: Multifunctional microelectronic fibers enable wireless modulation of gut-brain axis

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Abstract: The peripheral organs of the body are in a constant bidirectional cross-talk with the brain, that generates a cognitive map of body's physiological state which is vital for survival. This is exemplified by the gut-brain communication; wherein hormonally and neurally mediated signals emerging from the abdominal viscera transduce metabolic information to the brain for maintaining energy homeostasis. Although these internally arising gut-to-brain sensory cues are consciously imperceptible, recently they have been shown to influence neurocognitive processes such as motivation and affect. However, probing and understanding critical brain-body circuits in behaving animal models presents a neurotechnology challenge due to contrasting design criteria imposed on the implantable devices by drastic anatomical differences between the skull-encased brain tissue and mobile, delicate peripheral organs. Seeking inspiration from nerve fibers, we design a soft, flexible polymer fiber-based organ-brain neurotechnology. Particularly, our approach yields hundreds of meters of flexible polymer filamentary probes integrating microscale light emitting devices, thermal sensors, microelectrodes, and microfluidic channels. The ability to process thermoplastic elastomers with the same route enables deterministic tunability of device mechanics and allows probes for targeting deep-brain structures and the murine intestine. We custom design a light-weight Bluetooth based wireless control circuit, NeuroStack, that offers bidirectional wireless control and real-time programmability of in-fiber microdevices along with an intuitive user interface. The brain fibers offer microfluidic gene delivery for cell-type specific optogenetic neuromodulation, single-neuron recordings, thermometry, and tetherless control of mesolimbic reward pathway. The soft gut fibers grant access to anatomically challenging and delicate intestinal lumen, allowing intraluminal

optofluidic control of sensory epithelial cells that guide feeding behaviors. Using this new technology, we uncover that optogenetic stimulation of vagal afferents from the intestinal lumen is sufficient to drive reward behavior in untethered mice.

Disclosures: A. Sahasrabudhe: None. **L. Rupprecht:** None. **S. Orguc:** None. **D. Bohorquez:** None. **P. Anikeeva:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.04/R6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DoD SCIRP-CTA grant FY21

Title: Effect of Acute Genital Nerve Stimulation on Bowel Pressures in Individuals Living with Spinal Cord Injury

Authors: *R. F. HOEY[1,4], L. KORTY[1], A. BINKO[1], R. FASS[2,4], D. GUNZLER[3,5], M. MOYNAHAN[4], E. STITTS[1], J. WILSON[1], D. BOURBEAU[2,4,6], K. D. ANDERSON[1,4]; [1]Physical Med. and Rehabil., [3]Med. Admin., [2]MetroHealth Syst., Cleveland, OH; [4]Physical Med. and Rehabil., [5]Case Western Reserve Univ., Cleveland, OH; [6]VA Northeast Ohio, Cleveland, OH

Abstract: Among the many complications that occur after spinal cord injury (SCI), neurogenic bowel dysfunction is common (up to 95% of people require intervention) and in need of more research. Fecal incontinence is a consequence of SCI that substantially reduces participation in daily life. Even if fecal incontinence episodes are infrequent, those experiences can drive long term anxiety, worry, and reduction in quality of life (QOL) after SCI. Genital nerve stimulation (GNS) uses non-invasive surface electrodes to apply electrical stimulation to the sensory branch of the pudendal nerve (genital nerve) and strongly inhibits hyper-reflexive bladder contractions after SCI. Two small pilot studies have tested GNS on bowel function after SCI but have shown mixed results. Therefore, we combined GNS and anorectal manometry (ARM) with the goal of determining if GNS can change anorectal function. By collecting a broad range of outcome data, specified below, we will determine if GNS affects anorectal function and if any functional characteristics are predictive of GNS responsiveness. The London Classification protocol is being used to collect ARM data regarding anal sphincters and rectal function in an A-B-B-A repeated testing paradigm. Baseline data are collected prior to any stimulation, randomized first presentation of treatment (20 Hz) and sham (2 Hz) stimulation, and then retesting without stimulation; participants are blind to stimulation frequency. Additional data are being collected via self-report (demographics, injury history, medical history, ISCI Bowel Function BDS v2.1, SCI QoL BMD, and current medications) and clinical examination (ISNCSCI neurologic evaluation). Eligibility criteria include: SCI at or above T12, AIS A-D (goal of n=26 A-B, n=26

C-D, total n=52; M and F), over 18 yrs old, and ability to respond to GNS. To date there have been 6 participants enrolled with 4 participating in the ARM component. Reasons for attrition include: not tolerating the stimulation (1), and not demonstrating a reflex response to stimulation (1). Enrollment is ongoing, and preliminary results (n=4) suggest that GNS does influence ARM outcomes in a manner that may promote fecal continence (increased resting anal pressure and increased squeeze pressure). Because both resting anal pressure (internal anal sphincter) and squeeze pressure (external anal sphincter) show an increase, we postulate that GNS may improve function of both the internal and external sphincter after SCI. If GNS is effective at improving fecal incontinence, it will provide a non-invasive and inexpensive stimulation modality that could improve the QoL for many people after SCI.

Disclosures: R.F. Hoey: None. **L. Korty:** None. **A. Binko:** None. **R. Fass:** None. **D. Gunzler:** None. **M. Moynahan:** None. **E. Stitts:** None. **J. Wilson:** None. **D. Bourbeau:** None. **K.D. Anderson:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

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Program #/Poster #: PSTR079.05/R7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01-NS104291
Pennsylvania State Funds for Spinal Cord Injury Research

Title: Effects of Respiratory Training on Pre-phrenic Interneurons After Spinal Cord Injury

Authors: *K. SCHARDIEN[1], T. FORTINO[2], M. RANDELMAN[2], G. CALABRESE[3], A. HALL[4], S. SHARPLES[3], G. B. MILES[5], L. ZHOLUDEVA[6], M. A. LANE[7];
[1]Drexel Univ. Col. of Med., PHILADELPHIA, PA; [2]Drexel Univ. Col. of Med., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Univ. of St Andrews, St Andrews, United Kingdom; [4]Drexel University, Col. of Med., Philadelphia, PA; [5]St. Andrews Univ., St. Andrews Scotland, United Kingdom; [6]Gladstone Inst., Gladstone Inst., San Francisco, CA; [7]Drexel Univ. Col. of Med., Drexel Univ., Philadelphia, PA

Abstract: Spinal cord injury (SCI) often leads to a debilitating loss of function, with approximately 60% of injuries occurring at the cervical level. This disrupts respiratory pathways, posing life-threatening risks. However, there is significant evidence for spontaneous plasticity that contributes to partial functional recovery. Spinal interneurons play a crucial role in this plasticity, adapting their connectivity to establish new neuronal pathways. Moreover, activity-based therapies such as rehabilitation have shown promise in further enhancing plasticity by targeting these interneuronal pathways. In this study, our aim was to investigate the involvement of a specific subset of spinal interneurons in both spontaneous and therapeutically-driven plasticity. Although numerous spinal interneuron subtypes have been identified, their

contribution to respiratory plasticity following injury has remained limited. Expanding upon our previous studies investigating the contribution of excitatory, pre-motor V2a interneurons to neuroplasticity after spinal cord injury (SCI), the present study aimed to delve into the involvement of inhibitory and modulatory pre-motor interneurons—specifically V1 and V0c—in plasticity following high cervical SCI. Our study utilized a transgenic mouse model to evaluate the contribution of these interneurons to the phrenic network in both intact and injured states, with and without respiratory activity-based therapy involving 'intermittent hypoxia' or 'intermittent hypercapnia'. Transgenic mice received a lateral left hemisection at the second cervical segment (C2), denervating the ipsilateral spinal phrenic motor circuit (C3-C5/6) that controls the diaphragm - the primary muscle of inspiration. One week post injury, mice underwent respiratory training, consisting of 120 minutes of repeated normoxia, hypoxia, or hypercapnia cycles, once a day, 5 days a week, for 4 weeks. One-month post-injury, a transsynaptic retrograde tracer - pseudorabies virus - was applied to the left hemidiaphragm to label motor and spinal interneurons within the phrenic motor network ipsilateral to injury. Respiratory function was assessed using diaphragm electromyography in both cohorts. Immunohistochemistry was used to assess the extent of the lesion and to map the phrenic network. Preliminary analysis revealed increased interneuronal connectivity within the phrenic network following respiratory training. These data are the first to assess contribution of these specific interneuron subtypes to plasticity post SCI and training allowing for future considerations in harnessing a potential therapeutic for SCI.

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Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

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Program #/Poster #: PSTR079.06/R8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS104291
NIH F31 NS125975
F32 NS119348
CIRM DISC2-14180

Title: Transplanted human spinal interneurons functionally integrate with the injured cervical spinal cord

Authors: *L. ZHOLUDEVA[1], T. FORTINO[2], M. A. LANE[3], T. C. MCDEVITT[1], D. SRIVASTAVA[1];
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Abstract: Advances in cell therapies offer new promise for some of the most devastating neural injuries like spinal cord injury (SCI). One particular type of neuron - the spinal V2a interneuron - has been implicated as a key component in plasticity and therapeutically driven recovery post-SCI. In this study, we engineered V2a spinal interneurons (SpINs) from human induced pluripotent stem cells and tested their ability in forming functional synapses with injured motor networks. We used a clinically-relevant cervical contusion SCI in adult rats that results in damage to the phrenic motor network and impaired breathing to test integration, functional connectivity and overall contribution to respiratory recovery mediated by transplanted V2a SpINs. Single cell and nucleic sequencing were used to characterize differentiated cells prior to- and post-transplantation into SCI, revealing intriguing plasticity post-transplantation. Neuroanatomical tracing and immunohistochemistry were performed to demonstrate transplant integration and synaptic connectivity with injured host networks, and diaphragm electromyography was used to assess functional recovery of the injured phrenic network. Optogenetic activation of transplanted human V2a SpINs revealed functional synaptic connectivity to injured host circuits and improved diaphragm activity. Optogenetic activation of host supraspinal pathways revealed functional innervation of host neurons with transplanted cells. These studies are the first to 1) engineer human spinal V2a interneurons as an intended therapeutic product, and 2) demonstrate functional integration of human SpINs with injured respiratory pathways post-SCI. Having rigorously established improvement in diaphragm muscle activity with objective metrics, this strategy holds great promise to establish motor recovery post-SCI.

Disclosures: L. Zholudeva: None. **T. Fortino:** None. **M.A. Lane:** None. **T.C. McDevitt:** None. **D. Srivastava:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.07/S1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH
VA

Title: Spike-timing dependent plasticity in awake adult rats

Authors: *S. GAIKWAD[1], Y. CHEN[2], T. M. VAUGHAN[2], J. CARP[3], M. OUDEGA[4,5], J. WOLPAW[3], M. PEREZ[4,5];
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Abstract: Spike timing-dependent plasticity (STDP) has been successfully used to improve functional recovery in humans with spinal cord injury. Here, we hypothesized that STDP-like plasticity can be elicited in awake adult Sprague Dawley rats using similar procedures to those used in humans. Anesthetized rats were implanted with stainless steels screws in the skull over the hindlimb area of the left motor cortex for cortical stimulation, with a nerve cuff around the posterior tibial nerve for peripheral nerve stimulation, and with fine wire electrodes in the right soleus muscle for electromyographic recordings. During STDP, descending volleys elicited by cortical stimulation were timed to arrive 2.5 ms before (STDP+) or 15 ms after (STDP-) the arrival of antidromic volleys elicited in spinal cord motor neurons by stimulation of the posterior tibial nerve in two randomized sessions during different days. Interstimulus interval between cortical and peripheral nerve stimulation were calculated by measuring central and peripheral conduction time using the latency of the maximal motor response (M-max=1.2±0.2 ms), H-reflex (5.5±0.8 ms), and MEPs (6.3±0.3 ms) in the soleus muscle. Animals received 180 paired pulses. Motor evoked potentials (MEPs) in the soleus muscle were measured before, immediately after, and up to 40 min after both protocols. We found that MEPs size increased 10 min (153±29%), 20 min (130±29%), 30 min (137±17%), and 40 min (147±17%) after STDP+ compared with baseline. In contrast, MEP size deceased 10 min (83±24%), 20 min (74±26%), 30 min (77±7%), and 40 min (72±15%) after STDP- compared with baseline. Note these results were independently replicated in groups of male and female Sprague Dawley rats. These findings suggest that STDP-like plasticity can be elicited in intact awake adult rats, providing a model for testing neural mechanisms and combinatorial strategies to enhance functional restoration following spinal cord injury.

Disclosures: S. Gaikwad: None. **Y. Chen:** None. **T.M. Vaughan:** None. **J. Carp:** None. **M. Oudega:** None. **J. Wolpaw:** None. **M. Perez:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.08/S2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shriners Pediatric Research Center

Title: Combined chemogenetic motor cortex stimulation and neurotrophin-3 treatment alleviate spasticity and improve forelimb function after cervical spinal cord injury

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Abstract: Spinal cord injury (SCI) disrupts supraspinal control of spinal networks and often impairs sensorimotor processing in the spinal cord, resulting in severe functional impairments. Further, this can also lead to hyperreflexia and spasticity, which occur in more than 75% of individuals with chronic SCI. Effective therapeutic strategies that target both recovery and spasticity reduction are crucial for enhancing the quality of life in these individuals. This study explored the combined effects of chemogenetic motor cortex stimulation (CMCS) and neurotrophin-3 (NT-3) treatment on spasticity and hand function in cervical SCI. We hypothesized that CMCS and NT-3 would enhance plasticity, restore excitatory and inhibitory balance, and improve functional outcomes. In this rat study, we manipulated neuronal activity in the forelimb motor cortex by injecting excitatory DREADDs (AAV2-hM3Dq) or control (AAV2-mCherry) bilaterally. A week later, we induced a 200Kd contusion at the C5 segment and injected either human NT-3(AAV2-retro-NT3-eGFP) or eGFP (AAV2-retro-eGFP) into the distal forelimb muscles. After two weeks, rats underwent chronic CMCS with CNO (2mg/kg) for four weeks. We assessed skilled hand function, using IBB, grooming, and forelimb locomotor kinematics, while spasticity was evaluated using electrophysiological measures of H-reflex frequency-dependent depression, and reflex responses. Histological analysis was conducted to assess axonal regrowth and neuronal survival. The combined treatment significantly improved skilled hand function compared to the control groups. Animals receiving CMCS and NT-3 exhibited enhanced dexterity and increased grooming. Detailed kinematic analysis of the forelimb during locomotion showed more extended shoulder and elbow joints on average in the treatment group. Importantly, this combined treatment effectively reduced spasticity, as indicated by a significant decrease in muscle tone and reflex hyperexcitability. Histological analysis revealed increased axonal regrowth and neuronal survival in the treatment group, suggesting a synergistic effect of the combined therapy. These findings highlight the therapeutic potential of combining CMCS with NT-3 treatment for cervical SCI. They improve hand function and reduce spasticity, addressing key aspects of functional recovery. The observed regenerative effects suggest that this combined therapy may facilitate repairing and rewiring damaged neural circuits, leading to improved motor outcomes after cervical SCI. Further research is needed to understand mechanisms and optimize treatment protocols for clinical translation.

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Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.09/S3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS VA

Title: Reticulospinal Contributions to Intrinsic Muscles of the Foot in Humans

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Abstract: Electrophysiological studies in monkeys show that motor neurons innervating the intrinsic muscles of the foot receive strong corticospinal input compared to other hind limb muscles. However, the relative contribution of other descending motor pathways, such as the reticulospinal tract, to intrinsic foot muscle motor neurons remains poorly understood. The goal of our study was to examine the StartReact response, an involuntary release of a planned movement via a startling stimulus that engages the reticulospinal tract, by measuring reaction times from electromyographic activity in the abductor hallucis (AbH) during isometric flexion and abduction of the large toe. We measured reaction time during the presentation of a visual cue, a visual and auditory cue (80 dB, 500 Hz, 50 ms), and a visual and auditory startling cue (120 dB, 500 Hz, 50 ms). We found that the AbH reaction time during a visual cue was 252±55.6 ms during toe flexion and 264±24.2 ms during abduction. The reaction time during a visual and auditory cue was 207±41.2 ms during toe flexion and 218±25.7 ms during abduction and during a visual and auditory startling cue was 162±33.5 ms during toe flexion and 180±27.3 ms during abduction. To our knowledge these findings provide the first evidence for a contribution of the reticulospinal tract to the control of the foot in humans during toe movements.

Disclosures: R. Powell: None. **M. Perez:** None. **S.N. Baker:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.10/S4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01HL146114

Title: Cervical spinal cord injury results in changes in diaphragm neuromotor control in awake rats

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Abstract: Cervical spinal hemisection at C_2 (C_2SH) is a well-characterized model of spinal cord injury used to study neuroplasticity in the recovery of phrenic motor neurons (PhMN) and diaphragm muscle (DIAm) activity post injury. Neuromotor control of the DIAm involves three phases: motor unit recruitment, sustained motor unit recruitment, and derecruitment of motor units. These three neuromotor phases of breathing map onto well-known neural phases of breathing such as inspiration, post-inspiration, and expiration. The goal of this study was to

determine the impact of C_2SH and post-injury neuroplasticity on these three phases of DIAm neuromotor control. In the present study, we recorded bilateral DIAm EMG activity in awake female and male Sprague-Dawley rats before and at 14 days (D14) after C_2SH (right side) during eupnea and exposure to 7% CO_2. On both left (intact) and right (C_2SH) sides, we estimated the duration of motor unit recruitment, sustained recruitment, and derecruitment by quantifying signal stationarity of the DIAm EMG. Additionally, we evaluated magnitude (square root of the sum of squares during DIAm activity), burst duration, respiratory rate, and duty cycle of DIAm EMG activity. We found that by D14 post-C_2SH, ipsilateral DIAm EMG activity was reduced by ~35% compared to pre-C_2SH (n = 7; reductions in both magnitude during eupnea), while DIAm EMG on the intact contralateral side increased by ~50%. Respiratory rate increased by ~40% post-C_2SH, with duty cycles remaining at ~85%. On both sides of the DIAm, the durations of motor unit recruitment and derecruitment were not affected by C_2SH (~ 55 ms and ~65 ms, respectively during both eupnea and hypercapnia). By contrast, the burst duration on both sides was reduced by ~30% by decreasing the duration of sustained recruitment by 180 ms from a pre-injury value of ~500 ms. Overall, our results show clear evidence that ipsilateral DIAm activity is reduced post-C_2SH, while contralateral activity increases. Importantly, the duration of sustained motor unit recruitment decreased with C_2SH, while the durations of motor unit recruitment and derecruitment were unaffected. This clearly demonstrates neuroplasticity in the pattern of descending neural drive to PhMNs.

Disclosures: O.U. Khurram: None. **W. Zhan:** None. **M.J. Kantor-Gerber:** None. **C.B. Mantilla:** None. **G.C. Sieck:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.11/S5

Topic:

Support: NINDS
VA

Title: Corticospinal and Reticulospinal Contributions to Spasticity in Humans with Subacute Spinal Cord Injury

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Abstract: Evidence showed that the majority of individuals with subacute and chronic incomplete spinal cord injury (SCI) develop symptoms of spasticity (Sangari and Perez, 2022). Spasticity in the chronic stage of SCI has been associated to an imbalanced recovery of descending tracts characterized by aberrant facilitation of reticulospinal over corticospinal drive

(Sangari et al., 2019). However, the extent to which reticulospinal and corticospinal inputs contribute to spasticity in humans with subacute SCI remains unknown. We tested spasticity in the quadriceps femoris muscle in individuals with subacute (~1-month post-injury during inpatient rehabilitation) SCI using the Modified Ashworth Scale (MAS) and the Pendulum Test (first swing angle, FSA). Individuals with FSA<75deg were classified as spastic. We then evaluated maximal voluntary contraction (MVC) in the quadriceps muscle during isometric knee extension, and quantified corticospinal connectivity through Motor Evoked Potentials (MEP) at rest and during a small (10%MVC) voluntary quadriceps contraction. Reticulospinal drive was indirectly assessed through a StartReact paradigm during an isometric knee extension task (Baker and Perez, 2017). The StartReact effect was measured as difference between the reaction time to a soft (80dB) versus a loud acoustic stimulus (120dB, Choudhury et al, 2019). Measurements were also acquired in a group of age-matched control subjects. We found that MVC was reduced to a similar extent in SCI individuals with and without spasticity compared to control subjects. MEP were also reduced in both SCI populations compared to controls. However, the StartReact effect was significantly larger in spastic compared with non-spastic SCI participants ($p = 0.029$). Our results indicate that presence of spasticity in the subacute phase of SCI is likely associated with increased reticulospinal input.

Disclosures: D. De Santis: None. **M.A. Perez:** None.

Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.12/S7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: dhip campus-bavarian aim

Title: Preserved common synaptic inputs but altered distribution of motor unit action potentials innervating functionally paralyzed muscles

Authors: *D. SOUZA DE OLIVEIRA[1], P. BAYER[1], M. PONFICK[2], M. OSSWALD[1], D. BRAUN[1], A. CAKICI[1], T. KINFE[1], A. DEL VECCHIO[1];
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Abstract: Spinal cord injuries (SCIs) are diverse, and the neurophysiological changes after the injury are still not well understood. Here, we investigated the mechanisms the brain and motor neurons undergo to adapt after the injury by looking into motor unit (MU) neural and peripheral properties. For that, we applied high-density surface electromyography (HD-sEMG) grids on the forearm of healthy (control = 12) and chronic complete SCI individuals (SCI = 8). We recorded their muscle activity while they attempted 8 types of hand movements (flexion and extension of individual digits, grasp, two- and three-finger pinches) instructed by videos of a virtual hand. By

decomposing HDsEMG into individual MUs, we analyzed: distribution of MU territories within the muscles, MU area and number of high activity regions (hotspots), and common neural input, through a factorization analysis on the smoothed discharge rates. We found that the MUs territories are, on average, less spread in SCI (13.6 ± 5.2mm) compared to the control (17.9 ± 7.7mm), which implies fewer functional muscles in SCI (generalized linear mixed model: p = 3e-5). The area of the individual MUs was found higher in SCI (SCI: 3.5 ± 3.3cm^2, control: 2.7 ± 1.8cm^2; p = 0.008), with more dispersed MU activity in this group, i.e., more hotspots. This might indicate reinnervation/collateral sprouting. The neural control of MUs in SCI is explained by two main manifolds (neural modules), corresponding to flexion (flex) and extension (ext) of the digits as in the control group. By performing a cross-correlation between each of these modules and the virtual hand kinematics, we found a lower correlation in SCI (median: SCI - flex= -0.60, ext= 0.52; control - flex= -0.83, ext= 0.78) and a similar lag between the groups (SCI - flexion= 261ms, ext= 127ms; control - flex= 324ms, ext= 174ms). Despite the lower correlation in SCI, MU activity is still task-modulated. The comparable time delay between MU spike trains and the virtual hand kinematics across groups indicates that the synaptic input to the spinal motor neurons might be preserved. Overall, we show that individuals with SCI can still control their muscles, even in the absence of movement. The changes after the injury seem to happen mostly at the peripheral level, with changes in MU territories distribution and innervation, indicated by area and hotspots. These properties might be useful as potential biomarkers of motor recovery/adaptation and residual control of muscles. Understanding the neural control of movement after SCI is essential for a more adequate classification of injuries and the development of recovery strategies.

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Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.13/S8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01DK129194

Title: Sexually different spinal circuits innervating external urethral sphincter in spinal intact (SI) and spinal cord injured (SCI) mice

Authors: *S. KARNUP[1], M. HASHIMOTO[2], K. CHO[2], J. BECKEL[1], W. DEGROAT[1], N. YOSHIMURA[2];
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Abstract: Spinal cord injury (SCI) causes impairment of coordination between bladder and external urinary sphincter (EUS) leading to reorganization of reflex voiding. Neural circuits

responsible for reflex voiding are in lumbar-sacral segments of the spinal cord. L6-S1 contain (a) dorsolateral nucleus (DLN) with EUS-projecting motoneurons (EUS-MNs) and (b) dorsal commissure (DCM) with interneurons (INs) presynaptic to EUS-MNs. L4-L3 contain a population of propriospinal interneurons (PPNs) also presynaptic to EUS-MNs. To quantitatively assess differences in EUS spinal circuits between [a] males and females and [b] spinal intact (SI) and SCI animals, we traced circuits with PRV and FluoroGold (FG) injected to EUS. In ChAT-GFP mice retrograde trans-synaptic tracing of INs and PPNs was performed with PRV614 encoding RFP. PRV was injected to EUS 6 weeks after spinal cord transection, when reflex voiding recovered. FG was used to separate EUS-MNs from motoneurons innervating *musculus ishiocavernosus* (IC) also present in DLN. We found that DLN contains two morphologically distinct cell types. One of them (BB-MNs) has elongated bipolar soma on the grey/white matter border (g/w) and dendrites directed medially and laterally along g/w with branches deep in ventral or lateral funiculi. Only these cells were labeled with FG indicating their EUS-MN identity. Another type of DLN cells (RM-MNs) displayed no preferable dendritic branching and a large rounded multipolar soma rarely labeled with FG, indicating that RM-MNs innervate the IC. Number of MNs of both types in males was twice as large as in females. SCI caused partial loss of MNs in males and females in all spinal nuclei. After SCI, males showed a 4-fold rise in number of RFP labeled cells in retro-dorsolateral nucleus (RDLN) innervating the hind limb. This suggests [a] an existence of direct synaptic interactions between spinal nuclei and [b] post-SCI increase of local non-specific inputs to EUS-MNs. Number of INs and PPNs deferred between males and females: in SI males these numbers were ~10 times larger than in SI females. In males SCI caused two-fold decrease of INs and PPNs numbers, whereas in females a decrease was insignificant. The main conclusions from the obtained data are: (1) sexually dimorphic spinal EUS circuits in males comprise substantially more neurons of all relevant types, (2) EUS-MNs obtain most of the excitatory input from their dendrites within or near the funiculi, but not from the central grey matter, (3) SCI leads to non-specific loss of neurons and to occurrence of random local connections, which may cause the impairment of coordination between specialized cell types involved in SCI-induced LUT dysfunction.

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Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.14/S9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NSF DARE 1933751
NIH R01NS096971

Title: Preservation of cortical population dynamics after spinal cord injury

Authors: *K. A. MOXON[1], G. DISSE[2], X. TANG[1], B. NANDAKUMAR[3], Z. ZANG[1], Z. KONG[1];
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Abstract: Human and animal subjects with various neurological conditions can control neuroprosthetic devices using their own cortical signals with surprising ease, even years after loss of sensorimotor function. However, the underlying neural computations that explain this phenomenon have not been elucidated. To address this, we assessed the longitudinal impact of a clinically-relevant contusion model of spinal cord injury (SCI) on single-neuron encoding and population-level dynamics in the rat motor cortex (M1) during a postural task. We recently found that this task, in which animals react to unexpected perturbations in the lateral plane, elicits significant responses in the trunk and hindlimb representations in M1 in uninjured animals. Additionally, given recent evidence that physical rehabilitation therapy after injury supports improved postural control through significant M1 reorganization, we evaluated the impact of therapy on these outcomes. We found that, in conjunction with expected postural deficits, SCI led to significant a reduction in cortical encoding on a single-neuron level. Physical rehabilitation modestly attenuated the severity of both of these behavioral and cortical encoding effects. However, population-level dynamics continued to sufficiently predict the animal's position in space after injury, supporting a sustained role of the cortex in the encoding of postural control even after SCI. To determine if this sustained predictive ability was due the adoption of novel encoding strategies or the preservation of pre-injury dynamics, we compared the M1 population dynamics at multiple timepoints after SCI to the dynamics observed prior to injury using canonical correlation analysis. Surprisingly, we found that population dynamics remained stable for months after SCI. Stability of population dynamics despite changes to the neural system on the single-neuron level may explain why injured individuals are able to so readily learn neuroprosthetic control. Instead of adopting arbitrary, novel computations that differ from existing neural structure, individuals can utilize pre-existing repertoires to control these devices after neurological injury.

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Poster

PSTR079. Spinal Cord Injury: Plasticity—Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.15/S10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life - Spinal Cord Research Foundation (WFL-US-07/19:199)
The Yerger NeuroRobotics Research Fund, Jackson MS
Wilson Research Foundation, Jackson MS

Title: Distinguishing reflex from non-reflex responses elicited by transcutaneous spinal stimulation targeting the lumbosacral cord

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Abstract: The goal of neuromodulation with transcutaneous spinal stimulation (TSS) is to depolarize posterior roots over lumbosacral or cervical segments and thereby provide input to the spinal cord in order to enable movements or reduce spasticity. Beside reflex responses, several reports suggest that TSS may also depolarize anterior roots eliciting direct motor responses with pulses of different durations. The aim of this study was to characterize different types of responses elicited by unipolar TSS over the lumbosacral region using 50 and 1000 µs pulse durations. Additionally, we determined the consistency of response types over 2-3 months and whether their appearance differed between unipolar and bipolar electrode configurations. In 12 neurological intact participants (6 women), unipolar TSS was applied with the cathode (5x5 cm) placed over T11/T12 spinal processes and two electrodes (5x10 cm) placed paraumbilically and interconnected as the anode. For bipolar TSS, the cathode was moved 2.5 cm down and the anode (5x5 cm) was placed 5 cm above the cathode. EMG signals were collected from 12 dominant and 4 non-dominant leg muscles. TSS was applied in a paired-pulse paradigm at 5 interstimulus intervals (ISI, 25, 50, 100, 200, 400 ms) and 3 incremental stimulation intensities for each pulse duration (50, 1000 µs). Based on the visual presence or absence of paired-pulse suppression, responses were categorized into posterior root reflexes (PRR), direct motor responses, and mixed responses. Then we calculated a paired-pulse ratio (second to first responses) that best discriminated reflex from non-reflex responses. The prevalence of PRRs with unipolar TSS was 89% across both pulse durations, whereas the prevalence of motor responses was 7% and mixed responses 4%. The distribution of response types was not different between 50 and 1000 µs pulse durations (PRR: 88%/89%, motor: 8%/6%, mixed: 3%/5%, respectively; $X(2)=1.29$, $p=.52$). The paired-pulse suppression ratio at 25-ms ISI was 0.090 (0.11) for PRRs compared to ratios of 0.763 (0.22) for mixed responses and 0.941 (0.12) for direct motor responses. Paired-pulse ratios between 0.51 and 0.59 classified responses into PRRs and motor/mixed types with 100% sensitivity and 100% specificity. The conversion among different response types between two sessions was not significantly different (McNemar's test $p = .114$). With bipolar TSS, all responses were classified as PRRs. In conclusion, unipolar lumbosacral TSS mainly and consistently elicits PRRs independent of pulse duration, which can be reliably discriminated from non-reflex responses by paired-pulse ratios below 0.5 (25-ms ISI). Bipolar TSS exclusively elicits PRRs.

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Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.01/T1

Topic: D.02. Somatosensation – Pain

Support: Lundbeck S/A

Title: Establishment of a preclinical migraine model based on nitroglycerine (NTG)-induced sensitization of spinal trigeminal parabrachial (TPB) neurons in the anesthetized rat

Authors: *J. ALLARD[1], O. TOURY[2], A. ASUNI[4], F. GASTAMBIDE[4], B. BUISSON[3], B. HALL[4];
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Abstract: The spinoparabrachial pathway plays a major role in the development of chronic pain. Yet, its involvement in pain-related migraine has not been studied. Our aim was to establish a translational model for screening drug candidates against migraine, based upon electrophysiological measures of the activity TPB neurons and the ability of NTG to trigger migraine. Experiments were performed in isoflurane-anesthetized male Sprague Dawley rats. A concentric bipolar stimulating electrode connected to a current generator was aimed at the PB area. The upper cervical spinal cord was exposed after laminectomy for recordings. The search for TPB neurons was exclusively based on antidromic stimulations from the PB area. Only neurons with positive collision test innervating the peri-orbital region were included. Basal firing and evoked responses to mechanical (brush, Von Frey (VF) at 20-700 mN and pinch) and thermal (water jet (WJ) at 0-50 °C) stimulations of the receptive field were measured as number of action potentials (AP) for each neuron (1 to 3 per rat). General characteristics of lamina I (n=43) and lamina III-V (n=21) TPB neurons were obtained in a first experiment. The mean conduction velocity of lamina I neurons (mean, 3.8 m/s) was significantly lower than lamina III-V neurons (5.8 m/s). Neurons were polymodal nociceptors with the exception of heat-specific (1/43) and mechano-specific nociceptors in lamina I (2/43), and mechanoreceptors in lamina III-V (6/21). Basal firing was low and tended to be higher in lamina I compared with lamina III-V (median, 4.5 and 1.0 AP/min, respectively). Evoked responses were similar in lamina I and III-V, but for WJ at 50 °C, which was significantly higher in lamina III-V (median, 396 AP) than in lamina I (177 AP). In a second experiment, the effects of chronic NTG or corresponding vehicle (VEH) were measured on lamina I (18 VEH, 12 NTG) and lamina III-V (17 VEH, 14 NTG) neurons. Basal firing tended to be higher in NTG treated rats for both lamina I and lamina III-V neurons. Unexpectedly, evoked responses of lamina I neurons were comparable in NTG and VEH rats, whereas evoked responses of lamina III-V neurons were increased in NTG compared with VEH rats. The most pronounced differences between NTG and VEH were observed for VF 280 mN (median, 145 and 62 AP, respectively) and WJ 46 °C (293 and 126 AP, respectively). We here provide the first electrophysiological characterization of TPB neurons innervating the facial region. The sensitization of lamina III-V TPB neurons upon NTG treatment might represent one component of the generation of migraine sensation. Next steps include an assessment of known reference drugs to reverse this sensitization.

Disclosures: J. Allard: None. **O. Toury:** None. **A. Asuni:** None. **F. Gastambide:** None. **B. Buisson:** None. **B. Hall:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.02/T2

Topic: D.02. Somatosensation – Pain

Support: NIH 75N95019D00026

Title: Pharmacological characterization of rat models of vascular headache and migraine

Authors: *M. URBAN[1], Y. ZHANG[1], T. BERKMAN[1], E. DUGAN[1], K. BUBAN[1], J. HAGEDORN[1], A. DORIA[1], S. A. WOLLER[2], S. IYENGAR[2], T. HANANIA[1]; [1]PsychoGenics, Inc., Paramus, NJ; [2]NINDS, NIH/NINDS, Rockville, MD

Abstract: Rat models of vascular headache and migraine have been described in which facial allodynia is produced following systemic administration of nitric oxide donors or direct dural infusion of inflammatory soup. In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we evaluated a variety of analgesic compounds to characterize the pharmacology associated with preclinical models of vascular headache and migraine. Adult male and female Sprague Dawley rats were used in these studies, and models of vascular headache and migraine involved administration of the nitric oxide donor isosorbide dinitrate (ISDN; 10 mg/kg, i.p.) or dural infusion of inflammatory soup (IS; 2 mM serotonin, histamine, bradykinin, 0.2 mM PGE2). Facial allodynia was measured by applying calibrated von Frey filaments to the periorbital region of the face and determining facial sensitivity thresholds (facial swipe/head withdrawal). Study groups were randomized, the investigators were blinded to treatment, and groups were sufficiently powered to identify statistically significant effects. Administration of ISDN or infusion of IS produced a transient facial allodynia which persisted for 1-2 hours. Pretreatment with the mu opioid agonist morphine sulfate (6 mg/kg) completely prevented the development of facial allodynia, while administration of the 5-HT1B/1D agonist sumatriptan (1 mg/kg) or CGRP receptor antagonist olcegepant (1 mg/kg) partially inhibited facial allodynia. In contrast, pretreatment with the NSAID naproxen (30 mg/kg) was ineffective in inhibiting facial allodynia. The data demonstrate that clinically effective treatments for headache and migraine can prevent the development of facial allodynia in rat models of vascular headache and migraine. Additional potential therapies for headache and migraine are currently being evaluated to further understand the pharmacology associated with these models, and to support the use of these models to accelerate the development of novel treatments for headache and migraine.

Disclosures: M. Urban: None. **Y. Zhang:** None. **T. Berkman:** None. **E. Dugan:** None. **K. Buban:** None. **J. Hagedorn:** None. **A. Doria:** None. **S.A. Woller:** None. **S. Iyengar:** None. **T. Hanania:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.03/T3

Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS104200

Title: Contribution of macrophages and iNOS to migraine-like behaviors induced by dural prolactin and repeated stress

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Abstract: Migraine impacts 15% of the global population but predominantly affects women. We have shown a role for prolactin in animal migraine models induced by either stimulation of the dura mater or repeated stress exposure. However, the location of action of prolactin is not fully known nor are its downstream mechanisms. Using von Frey filaments to measure periorbital mechanical thresholds, we found that conditional knockout of prolactin receptors in Nav1.8-expressing sensory neurons partially but significantly blocked the periorbital hypersensitivity caused by dural application of prolactin (5 μg) to female mice. This indicates that responses to dural prolactin are not mediated exclusively by sensory neurons. We thus hypothesized that prolactin acts in part through non-neuronal cells in the dura. Since prolactin is known to act on immune cells such as macrophages, we tested a role for these cells in this model. Depletion of macrophages using clodronate liposome injections before dural prolactin significantly blocked the prolactin responses. We further investigated whether prolactin induces responses through the activation of iNOS, an enzyme highly expressed in macrophages. Injection of the iNOS inhibitor AR-C102222 (AR-C; 15 mg/kg) significantly blocked the dural prolactin-induced responses. These findings indicate that both macrophages and iNOS contribute to the behavioral responses to dural prolactin. We have shown previously that repeated stress induces periorbital hypersensitivity and priming to a low-dose of the NO donor sodium nitroprusside (SNP; 0.1 mg/kg). To determine whether macrophages and iNOS contribute to repetitive stress-induced periorbital hypersensitivity and priming to SNP, stressed or control mice received clodronate liposomes or AR-C injection before repetitive stress exposure. Macrophage depletion in stressed mice significantly inhibited stress-induced periorbital hypersensitivity in both males and females. However, AR-C only blocked stress-induced migraine-like behaviors in females but not in males. In conclusion, this study demonstrates the involvement of prolactin receptors on sensory neurons, as well as a role for macrophages and iNOS in dural prolactin-induced periorbital hypersensitivity. In response to repeated stress, macrophages contribute to behavioral responses in both males and females while iNOS only plays a role in females. These findings highlight the crucial roles of macrophages and iNOS in stress and prolactin-induced periorbital hypersensitivity and reveal sex-specific differences in iNOS activity following stress.

Disclosures: H. Mei: None. **B. Mason:** None. **M. Burton:** None. **G. Dussor:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.04/T4

Topic: D.02. Somatosensation – Pain

Support: RTG 2660: Neural mechanisms of (mal)adaptive approach-avoidance behavior by Deutsche Forschungsgemeinschaft (DFG)

Title: Migraine and CGRP: a methodological study on CGRP levels in plasma, serum, tear fluid and saliva

Authors: *M. PATERNOSTER, S. LÖFFL, C. SOMMER;
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Abstract: Background/Aim: Migraine is a neurological disease affecting around 14% of the world population, with a higher occurrence in women than in men. Although the exact pathophysiology is not known, migraine is considered a neuronal excitability disorder where the trigeminovascular system seems to play a key role. The onset of a migraine attack is linked with an increase of pro-inflammatory molecules and neuropeptides, including Calcitonin Gene Related Peptide (CGRP); a potent vasodilator. Published data is not consistent in collection methods or analysis of CGRP levels in migraine patients. For neurobiological characterization, we compared CGRP levels in different sample types from patients with episodic and chronic migraine to those in healthy controls.
Methods: Here we present first data of a monocentric observational study. Our interim analysis includes 123 subjects divided into three groups (EM: episodic migraine; CM: chronic migraine; HC: healthy controls). For the quantitative determination of CGRP, we used an enzyme-linked immunosorbent assay (CUSABIO®, Wuhan, China). We assessed CGRP levels in serum, plasma, tear fluid and saliva. All samples were collected in a standardised way and kept at -80°C until analysed.
Results: Currently, we were able to analyse data from 123 subjects, divided in 72 EM patients (median age: 39 years; 61 female) and 15 CM patients (median age: 42 years; 15 female) and 36 HC (median age: 44 years; 27 female). Median migraine days per month were 4 days for EM patients and 15 days for CM patients. There is a correlation between serum and plasma CGRP levels in all groups (EM: $r = 0.767$; $p < 0.001$, CM: $r = 0.643$; $p = 0.018$, HC: $r = 0.673$; $p < 0.001$). There was a difference in plasma CGRP levels between CM and EM ($p = 0.034$) and CM and HC ($p = 0.001$). See table 1 for detailed data.
Conclusion: Early results indicate that plasma and serum CGRP levels are comparable. In addition, plasma CGRP levels differ among groups.

	Demographic data			CGRP concentrations (pg/ml)				
Groups (N)	**Age in years** *[Range]*	**Sex** (male/female)	**Migraine days per month** *[Range]*	**Plasma** *[Range]*	**Serum** *[Range]*	**Tear fluid left eye** *[Range]*	**Tear fluid right eye** *[Range]*	**Saliva** *[Range]*
HC (36)	44 [21-71]	8/28	/	3.476 *[1.836 – 21.278]*	4.074 *[1.688 – 22.454]*	939.909 *[139.360 – 6883.907]*	1433.204 *[104.410 – 7123.560]*	76.421 *[17.493 – 778.084]*
EM (72)	39 [21-65]	11/61	4 [0-10]	4.234 *[1.824 – 14.658]*	4.190 *[1.673 – 13.046]*	2385.133 *[143.456 – 17404.805]*	2149.977 *[96.816 – 17130.414]*	110.837 *[17.461 – 593.460]*
CM (15)	42 [21-62]	2/13	15 [10-26]	7.323 *[2.146-13.230]*	5.390 *[3.116 – 10.276]*	2161.152 *[264.418 – 69612.035]*	954.674 *[249.818 – 5677.209]*	75.715 *[26.334 – 717.465]*

Table 1
Demographic data of the cohort and CGRP concentrations in different sample types (EM = episodic migraine, CM = chronic migraine, HC = healthy controls)

Disclosures: M. Paternoster: None. **S. Löffl:** None. **C. Sommer:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Educational talks for TEVA.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.05/T5

Topic: D.02. Somatosensation – Pain

Title: The auditory radiation and migraines

Authors: E. KIPARIZOSKA[1], ***T. IKUTA**[2];
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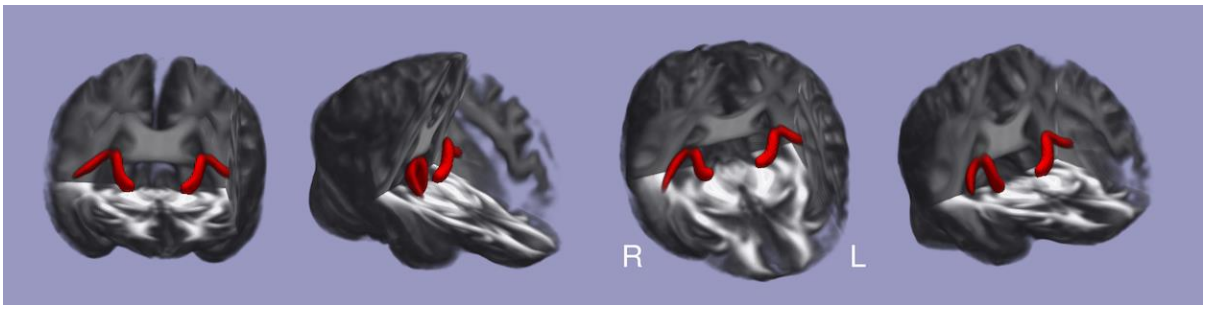
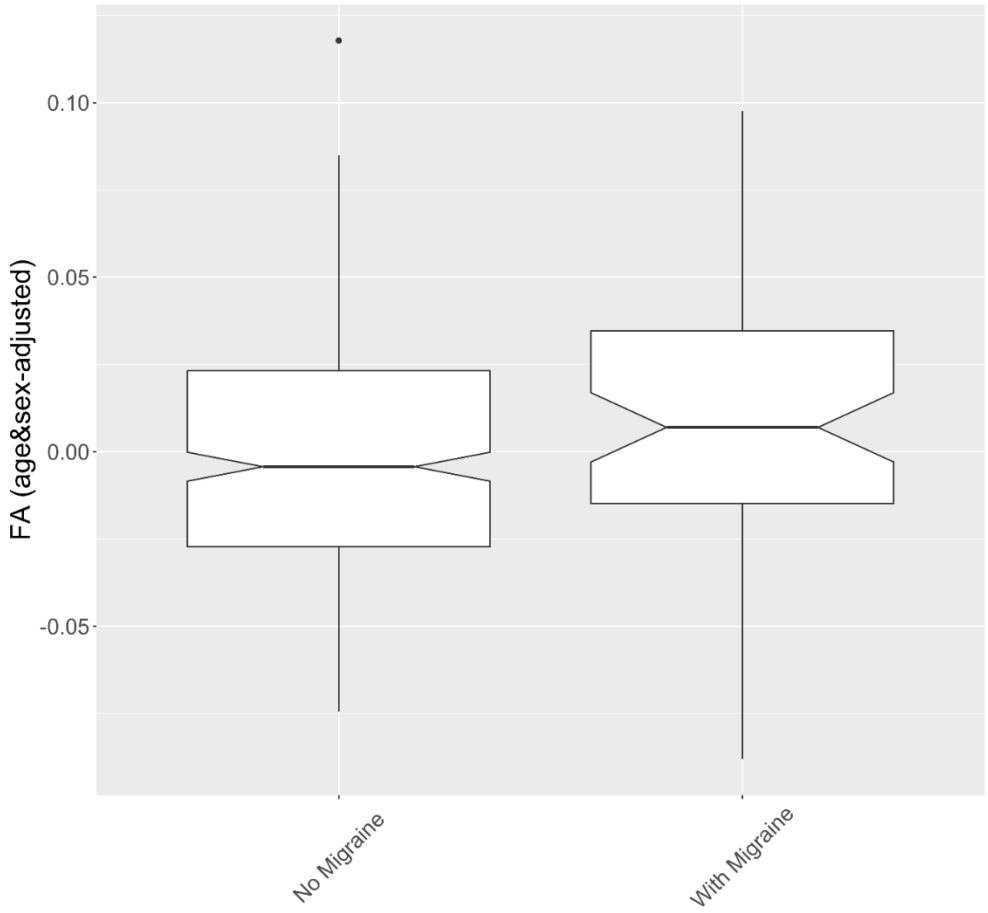
Abstract: While associations between migraines and hearing loss have been previously identified, there is still a lack of sufficient understanding regarding the relationship between migraines and hearing. Therefore, this study aimed to investigate the relationship between a history of migraines and the auditory radiations. Utilizing data from Nathan Kline Institute-Rockland Sample, we tested the association between the history of migraines and the integrity of the auditory radiation in 431 individuals. Using Probabilistic Tractography, the auditory radiation was extracted from Diffusion Tensor Imaging (DTI) data (Fig1). Fractional Anisotropy (FA) was used as the primary index to assess the integrity of the auditory radiation. The results revealed that individuals with a history of migraines exhibited greater integrity of the audiotyr radiations compared to those without a history of (Fig 2). It is suggested that higher auditory radiation integrity may correspond with migraines, ultimately correlating with an increase in hearing loss.





Disclosures: **E. Kiparizoska:** None. **T. Ikuta:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.06/T6

Topic: D.02. Somatosensation – Pain

Support: The McKnight Foundation
NIH Director's New Innovator Award
Lulu Merle Johnson Fellowship

Title: Investigating Local Field Potential Connectivity Patterns in a Thalamic-Driven Migraine Subnetwork

Authors: *M. JOHNSON, B. HING, I. HULTMAN, M. EBERLE, Y. FILALI, M. MATKOVICH, A. JIMENEZ, S. SRIVASTAVA, R. HULTMAN;
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Abstract: Migraine is one of the most prevalent disorders, affecting over 1 billion people worldwide. Migraine is characterized by dysfunctional sensory-related brain circuits that intersect pain, sensation, and affect. Functional imaging studies in humans have implicated individual brain regions such as the parabrachial nucleus (PBN), posteriorbthalamus (Po), mediodorsal (MD), ventroposteromedial (VPM), basolateral amygdala (BLA), central amygdala (CeA), and anterior cingulate cortex (ACC) in migraine. However, the connectivity patterns underlying the mechanisms by which such brain regions contribute to migraine remain elusive. Local field potential (LFP) activity across the brain provide insight into network-level dynamics that mediate behavior. In our study, we examined whether oscillatory patterns across the PBN, Po/MD/VPM, BLA/CeA, and ACC reflect an emergent migraine-related brain state on an individual and subnetwork-level. To address this question, we utilized an interdisciplinary, systems-based approach consisting of *in-vivo* microelectrode brain recordings to study LFP connectivity patterns across the brain in a calcitonin gene-related peptide (CGRP) mouse model of migraine and treated them with an anti-migraine drug, sumatriptan. After inducing migraine in male and female CD1 mice, we tested several migraine-related phenotypes including light aversion and spontaneous pain (squint). As a control, we treated animals with phosphate-buffered saline. Previously, we found directional flow of information from the amygdala to thalamic regions in the 2-7 Hz frequency band and increased spectral power in the Po and VPM in the same frequency band. We hypothesized that CGRP-treated animals would exhibit increased light aversive and squint responses and LFP power and coherence in thalamic regions would correlate with light aversion and squint response. During our studies, experimenters were blinded to treatment conditions and performed behavioral assays in replicates. We found that implanted animals (n=37) exhibited increased light aversion ($p<0.001$). Po and VPM spectral power in the 2-7 Hz frequency range and AMY-Thal coherence was correlated with XX and XX. Further, we found directional flow of information from the ACC to thalamic regions in the 1-6 Hz frequency band. ACC spectral power changes were observed across time. Finally, we found evidence for a potential thalamus-driven subnetwork during evoked-migraine. Overall, our findings provide evidence for thalamic-driven mechanisms in the pathophysiology of migraine and related phenotypes and the use of such brain networks as potential therapeutic targets.

Disclosures: M. Johnson: None. **B. Hing:** None. **I. Hultman:** None. **M. Eberle:** None. **Y. Filali:** None. **M. Matkovich:** None. **A. Jimenez:** None. **S. Srivastava:** None. **R. Hultman:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.07/T7

Topic: D.02. Somatosensation – Pain

Title: Grimace scale as a robust metric for nociception in a nitroglycerin (NTG)-induced mouse migraine model

Authors: A. WOBLISTIN, ***R. RABL**, L. BREZNIK, L. JAUK, M. DAURER, T. LÖFFLER, M. PROKESCH;
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Abstract: Migraine, with its associated headache and neurological symptoms, is a severely impairing condition affecting more than a billion people worldwide. Although migraine is one of the most common neurologic disorders, the neurophysiological causes and thereby potential intervention avenues, remain mostly unknown, highlighting the need for a fast turnaround model to study this condition. The nitric oxide donor nitroglycerin (NTG) induces severe migraine-like attacks in mice and humans alike. NTG was thus chosen to establish a murine migraine model. The antimigraine drug, sumatriptan, was used as a reference compound. To investigate the effects of acute and chronic NTG injection in 2-3 months old mixed sex C57BL6 mice, a behavioral test battery evaluating nociception followed by histological and biochemical analysis was performed. In detail, mice were tested after single or repeated injection of NTG and assessed for increased allodynia by grimace scale, grooming and hotplate tests as well as light sensitivity in the light/dark box. Subsequently, mice were sacrificed to histologically and biochemically investigate c-fos, CGPR and inflammation markers. In acute and chronically NTG-treated mice, the grimace scale analysis showed a strong increase in nociceptive responses that can be alleviated by co-injection of sumatriptan, similarly to what has been observed in humans. Interestingly, this effect could only be observed if mice were kept awake between the injection and the behavioral test through repeated handling. Additional assessment of behavior did not show any differences between NTG- and vehicle-treated mice. Although biochemical and histological analysis is still ongoing, the first results indicate an increase in c-fos and IL-1ß labeling in the medial prefrontal cortex of the brain. These results affirm the NTG-induced migraine model as a valid and fast system to study migraine pathology in mice. The grimace scale proved to be a strong indicator of nociception in NTG-treated animals.

Disclosures: **A. Woblistin:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **R. Rabl:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **L. Breznik:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **L. Jauk:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **M. Daurer:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **T. Löffler:** A. Employment/Salary (full or part-time):; QPS Austria GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time):; QPS Austria GmbH.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.08/T8

Topic: D.02. Somatosensation – Pain

Support: R01 NS 110863
R01NS120945
R37NS119012

Title: Progesterone receptors regulate sensory sensitivity

Authors: *S. JOSHI[1], J. WILLIAMSON[2], S. MOOSA[2], J. KAPUR[3];
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Abstract: Women develop chronic pain during their reproductive years more often than men. We tested whether brain progesterone receptor (PR) signaling regulates pain susceptibility. The studies used adult female C57Bl6 mice or from a transgenic colony of mice lacking PR expression in the brain (PRKO) and littermate wild-type (WT) mice. The mechanical sensory sensitivity (manual Von Frey monofilaments), thermosensitivity (48 ºC and 15 °C), and light sensitivity (light-dark box) were measured. During the estrous cycle, the paw withdrawal threshold was lower in animals in the estrus stage than in the diestrus stage, suggesting a role for reproductive hormones, estrogen, and progesterone. To evaluate the role of progesterone, we measured the pain threshold daily for four days in ovariectomized, estrogen-primed animals treated with progesterone (10 mg/kg). The pain sensitivity was measured for 4 days after the progesterone injection. The paw withdrawal threshold was lower 2 days later and stayed that way for the duration of the testing. A similar reduction was not observed in the vehicle-treated mice. We evaluated whether this reduction was due to the loss of analgesic effects of progesterone metabolite allopregnanolone (THP) or due to PR activation. THP (10 m/kg, sc) acutely (1 hr later) increased the pain threshold, but the THP and vehicle groups were indistinct on days 1-4 days after progesterone injection. On the other hand, treatment of mice with a specific PR agonist, segesterone (10 mg/kg, sc) reduced the paw withdrawal threshold. The pain threshold did not reduce in the PRKO after progesterone or segesterone administration. Furthermore, PR activation reduced the escape latency from the cold floor indicative of an increased cold sensitivity but had no effect on the tail flick latency and had a minimal effect on light sensitivity. Segesterone treatment also lowered the periorbital pain threshold. Finally, we evaluated whether PR activation altered experimental migraine. Segesterone and nitroglycerin (NTG) when administered sequentially, reduced pain threshold but not separately. These studies have uncovered a pain-regulating function of PRs. Thus, targeting PRs may provide a novel therapeutic avenue to treat chronic pain, including migraine, in women.

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Poster

PSTR080. Headache and Migraine

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Program #/Poster #: PSTR080.09/T9

Topic: D.02. Somatosensation – Pain

Support: NIH R01 Grant NS104110
UT Dallas BBS Internal Research Grant

Title: Modulation of HPA axis signaling as a treatment approach for migraine-like behavioral responses caused by repeated stress exposure

Authors: *Y.-Y. HU[1], R. R. SOUZA[2], A. N. AKOPIAN[3], C. K. MCINTYRE[4], G. O. DUSSOR[5];
[1]Neurosci., UT Dallas, Richardson, TX; [2]The Univ. of Texas at Dallas, Univ. of Texas at Dallas, Richardson, TX; [3]UT Hlth. Sci. Ctr., UT Hlth. Sci. Ctr., San Antonio, TX; [4]Univ. Texas at Dallas, Univ. Texas at Dallas, Richardson, TX; [5]Neurosci., Univ. of Texas At Dallas, Richardson, TX

Abstract: Stress is the most common trigger for migraine attacks, but the mechanisms underlying the influence of stress on migraine attacks remain unknown. The body responds to stressors through the release of glucocorticoids (GCs) and through behavioral changes to maintain homeostasis. However, migraine may be an adverse consequence of this glucocorticoid response. The purpose of these studies was to examine the involvement of GCs and the hypothalamic-pituitary-adrenal (HPA) axis in the migraine-like behavioral responses elicited by repeated exposure to stress. We have previously demonstrated that repeated restraint stress in mice induces evokes migraine-like behavioral responses as well as priming to the nitric oxide donor sodium nitroprusside (SNP). In this study, we used this stress model to examine the involvement of corticosterone (CORT), adrenocorticotropic hormone (ACTH), and α-melanocyte-stimulating hormone (α-MSH). Our findings indicate that the administration of metyrapone, a glucocorticoid synthesis inhibitor, blocked the migraine-like behaviors induced by stress. This outcome suggests a pronounced reliance on CORT synthesis for the behavioral responses but a lack of CORT also causes increased compensatory release of ACTH. To test whether ACTH or its breakdown products contribute to these effects, stressed animals were treated with either ACTH or α-MSH post-stress. Both caused a reduction in mechanical hypersensitivity and grimace scores during the post-stress phase as well as the priming phase. To determine a potential receptor mediating these effects, we administered THIQ, a melanocortin 4 receptor agonist, to animals after stress. THIQ alleviated stress-induced migraine-like behaviors in female mice. Additionally, we investigated the effect of administering CORT after stress and also observed a reduction in stress-induced hypersensitivity. Our findings reveal the essential role of changes in glucocorticoid levels in stress-induced behavioral responses in both male and female mice. Furthermore, an increase of ACTH levels, along with the subsequent cleavage product α-MSH, following stress exposure can also influence the hypersensitivity induced by stress. This study contributes to our understanding of the intricate relationship between stress and

migraine, potentially providing a novel therapeutic approach for treatment of stress- induced migraine attacks.

Disclosures: Y. Hu: None. **R.R. Souza:** None. **A.N. Akopian:** None. **C.K. McIntyre:** None. **G.O. Dussor:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.10/T10

Topic: D.02. Somatosensation – Pain

Support: NIH/NINDS R01NS126752-01A1

Title: Interaction between the endocannabinoid system and the β_2-adrenergic receptor in a formoterol-induced headache model

Authors: *I. L. PETERSON[1,2], E. LIKTOR-BUSA[1], K. KARLAGE[1], S. YOUNG[1], N. E. SCHOLPA[2], T. M. LARGENT-MILNES[1];
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Abstract: Headache disorders are considered public-health concern, with approximately 45 million individuals experiencing headache pain annually in the United States. Primary headache disorders (e.g., migraine) do not have a clear underlying cause; however, secondary headache disorders are linked to stroke, medication side-effects, medication overuse, infection, and brain tumors, etc. The chronic administration of formoterol, an FDA-approved β_2-adrenergic receptor agonist, has been shown in humans to induce headache, however the mechanism behind this has not been elucidated. Recent data indicated that disruption of endocannabinoid signaling at certain brain regions, like PAG can contribute to both headache induction and maintenance after medication overuse of triptans and opioids. Therefore, we hypothesize that endocannabinoid system might be involved in the occurrence of headache induced by formoterol treatment. Female C57bl/6j mice underwent either a laminectomy (T11 vertebra) or sham surgery and were treated with either vehicle (0.3% DMSO in saline) or formoterol (0.3mg/kg, 200µL/mouse, i.p.) daily starting 8 hours post injury. Formoterol treated mice in both sham and surgery groups exhibited periorbital allodynia starting 7 days post injury, continuing out to a 42-day time point. PAG was collected at 42 days and processed for immunoblotting and liquid chromatography-mass spectrometry (LC-MS). Decrease in CB1 receptor expression in the PAG was observed in the formoterol treated sham mice versus the vehicle treated shams. Preliminary LC-MS showed an increased level of anandamide in the PAG in formoterol treated groups. Based on these results, we suggest an interplay between the ARs and eCB system that will require further elucidation.

Disclosures: I.L. Peterson: None. **E. Liktor-Busa:** None. **K. Karlage:** None. **S. Young:** None. **N.E. Scholpa:** None. **T.M. Largent-Milnes:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.11/U1

Topic: D.02. Somatosensation – Pain

Support: CDMRP award W81XWH2120457

Title: Dual fatty acid hydrolase and TRPV1 inhibitor reduces inflammation and post-traumatic headache like symptoms induced by repetitive traumatic brain injury

Authors: *G. NAGARAJAN[1,2], J. WEN[1,2], M. TANAKA[1,2], Y. ZHANG[2,1];
[1]The Henry M. Jackson Fndn. for the Advancement of Military Med., Rockville, MD; [2]Dept. of Anatomy, Physiol. and Genet., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Trigeminal autonomic cephalalgia-like phenotype is one of the classifications of post-traumatic headache (PTH) that is observed in one third of clinical diagnosis with traumatic brain injury (TBI). It is well known that TBI induces widespread inflammatory response in the brain, however, inflammatory response is also observed in the peripheral trigeminal ganglion (TG) that in turn could cause PTH-like symptoms. Here, we focus on the neuroprotective effect of endocannabinoid, anandamide (AEA), which gets rapidly hydrolyzed by fatty acid amide hydrolase (FAAH) in an injured state. We hypothesized that augmenting AEA after an injury state would reduce inflammation and thereby reduce PTH-like symptoms. Two months old male C57BL/6 mice were subjected to repetitive injury induced by rotational acceleration, once a day for 4 days. Mice (n=6/group) were randomly assigned to treatment with either dual FAAH/TRPV1 inhibitor N-arachidonoyl-serotonin (AA-5-HT) or FAAH inhibitor PF-04457845 or vehicle. Drugs were administered 1 hr after the 1st impact and continued for 7 days. On 4 and 6 days post-injury (dpi), PTH like symptoms such as decreased periorbital sensitivity ($p< 0.01$) and increased grimace score ($p<0.05$) were observed. Further 7 dpi, qPCR results showed significant increase in gene expression of inflammatory markers (aif1, trem2, c1qa; $p<0.001$) in the nucleus trigeminal caudalis (TNC). While immunohistochemistry (IHC) revealed increased expression of iba1, FAAH and TRPV1 in the TG. Surprisingly, the FAAH inhibitor alone (PF-04457845) further increased proinflammatory markers in the TNC. However, treatment with dual inhibitor AA-5-HT significantly reduced the TBI induced inflammatory gene expressions in the TNC ($p<0.05$). Interestingly, IHC results showed that AA-5-HT treatment increased TRPV1 expression and reduced FAAH expression in the TG. In parallel to the reduced expression of inflammatory markers in the trigeminal regions, AA-5-HT significantly reversed TBI induced periorbital sensitivity ($p = 0.013$), and lowered the grimace score ($p=0.06$). The results from this study suggest that reversal of TBI induced inflammation in the trigeminal regions and PTH-like symptoms by AA-5-HT is likely in part through augmentation of endocannabinoid (anandamide) and desensitization of TRPV1 neurons involved in nociception.

Disclosures: G. Nagarajan: None. **J. Wen:** None. **M. Tanaka:** None. **Y. Zhang:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.12/U2

Topic: D.02. Somatosensation – Pain

Support: Defense Health Agency (0130-18-0003-00017)
Congressionalyy Directed Medical Research Programs (CDMRP) award (W81XWH2120457)

Title: Modulation of TRPV1 activity by endocannabinoid anandamide in the development and treatment of posttraumatic headache

Authors: J. WEN, ***M. TANAKA**, G. NAGARAJAN, Y. ZHANG;
Anatomy, Physiology, and Genet., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Posttraumatic headache (PTH) is one of the most common sequalae of traumatic brain injury (TBI) that causes prolonged symptoms in human patients. PTH resembles migraine-like phenotype, suggesting that activation of the trigeminovascular system might play a pivotal role. However, the exact mechanisms of PTH remain unclear and there is no therapeutic agent currently available. Given that augmentation of anandamide (AEA) by inhibition of its hydrolytic enzyme, fatty acid amide hydrolase (FAAH) has been shown to be protective in the animal models of TBI and to attenuate various types of pain that include migraine, we anticipated that inhibition of FAAH should be effective in the treatment of PTH. Using a repetitive TBI mouse model induced by the closed-head impact model of engineered rotational acceleration (CHIMERA; 4 impacts within 24-hour interval), we found increased cephalic mechanical allodynia at 7 and 11 days post-TBI. Unexpectedly, treatment with the FAAH inhibitor PF04457845 did not attenuate inflammation in the trigeminal system and had little effects on periorbital allodynia. To determine if the lack of efficacy is due to activation of the transient receptor potential vanilloid 1 (TRPV1) by AEA leading to abnormal sensitization of trigeminal neurons, we examined the effect of the TRPV1 antagonist SB-366791 in the FAAH knockout (KO) mice following TBI induction. Administration of SB-366791 (1 mg/kg, ip) starting at 1 hour after each impact and then continuing for 3 additional days (7 days in total) partially reduced periorbital allodynia in the FAAH wild type mice, but almost completely alleviated hyperalgesia in the FAAH KO mice. At 7 days post-TBI, the increased immunoreactivity of Iba1, FABP7, TRPV1 and CGRP in the trigeminal ganglion of the FAAH KO mice was significantly reduced by SB-366791 treatment. Several inflammation genes, *Trem2, Gfap,* and *Cd68* were upregulated in the trigeminal nucleus caudalis of the TBI animals and suppressed in the SB-336791 treatment group. These results suggest that TRPV1 signaling mediated by AEA is likely exaggerated by deletion of FAAH, and blockade of the TRPV1 activity can boost the pain suppressive effects of AEA in the FAAH KO mice. We are currently under investigation if the therapeutic effect of SB-366791 in the FAAH KO mice is also attributed to activation of cannabinoid receptors.

Disclosures: **J. Wen:** None. **M. Tanaka:** None. **G. Nagarajan:** None. **Y. Zhang:** None.

Poster

PSTR080. Headache and Migraine

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.13/U3

Topic: D.02. Somatosensation – Pain

Support: NINDS R01 NS130882
NIH-NIAAA Training Grant T32AA026577

Title: Delta opioid receptor activation blocks allodynia in a model of PACAP-induced headache

Authors: *E. MANGUTOV[1], I. DRIPPS[3], K. SIEGERSMA[3], R. BOCIAN[4], T. HALBESMA[3], A. A. PRADHAN[2];
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Abstract: Pituitary adenylate cyclase activating polypeptide (PACAP) is a known human migraine trigger and antibodies against the peptide and its receptor (PAC1) are being tested for the treatment of migraine. We have previously identified the delta opioid receptor (DOR) as a novel therapeutic target for headache disorders. However, it is still unclear how DORs regulate migraine-associated symptoms. Anatomically, DOR is expressed in regions that also express PACAP and PAC1. One of the aims of this study was to develop a mouse model of PACAP-induced headache, and to determine the effect of DOR agonist in this model. A further goal was to investigate cellular co-expression of DOR with PACAP and PAC1 receptor. To develop the PACAP model in mice, the effect of increasing doses of acute and chronic PACAP was assessed on mechanical responses measured by manual von Frey hair stimulation of the periorbital region. We also tested established headache therapies in this model, including sumatriptan, the calcitonin gene related peptide (CGRP) antagonist, olcegepant, and the DOR agonist, SNC80. Expression of DOR and the PACAPergic system was determined using in situ hybridization to identify co-expression of PACAP, PAC1, and DOR transcripts. The somatosensory cortex, hippocampus, trigeminal nucleus caudalis, and trigmeinal ganglia were analyzed. PACAP caused acute and chronic dose-dependent cephalic allodynia. Our maximum dose of PACAP was blocked by sumatriptan and DOR agonist SNC80, but not olcegepant. Correspondingly, in a model of chronic CGRP-induced allodynia, the PAC1 antagonist M65 was ineffective. There was some coexpression of PACAP and DOR in all brain regions but it was relatively low. In contrast, there was very high coexpression (>75%) of PAC1 and DOR in the somatosensory cortex, hippocampus, and trigeminal nucleus caudalis. We have developed a mouse model of PACAP-induced allodynia that responds to known migraine therapeutics. DOR agonists showed efficacy in this model, and a strong co-expression between PAC1 and DOR was observed in specific brain regions. Further investigations will determine the mechanistic relationship between DOR and PACAP-PAC1.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.01/U4

Topic: D.02. Somatosensation – Pain

Support: NIH grant NS038261

Title: Effects of astrocyte inhibition on amygdala neuronal functions in a model of neuropathic pain

Authors: ***M. MAZZITELLI**, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Pain is a clinically relevant global health care issue with limited safe and effective therapeutic options, creating a desperate need for new and improved analgesic strategies. A better understanding of pain mechanisms at all levels of the pain system is needed. The amygdala is a limbic brain region critically involved in the regulation of emotional-affective components of pain and in pain modulation. The central nucleus of amygdala serves major output functions and receives nociceptive information via the external lateral parabrachial nucleus (PB). While amygdala neuroplasticity has been linked causally to pain behaviors, non-neuronal pain mechanisms in this region remain to be explored. Neuroimmune signaling has been linked to the pathophysiology of various disorders, including pain. As an essential part of the neuroimmune system, astrocytes, which represent about 40-50% of glia cells within the central nervous system, are required for physiological neuronal functions, but in pathological conditions, astrocytes become activated (“reactive”), undergoing a series of structural and functional changes, which may have protective effects, but that remains to be determined for pain conditions. In this study, we assessed the contribution of astrocytic signaling to amygdala neuroplasticity in a model of neuropathic pain. Whole-cell patch-clamp recordings were performed from neurons in the laterocapsular division of the central nucleus of amygdala (CeLC) obtained from neuropathic rats (spinal nerve ligation, SNL). Incubation of brain slices with fluorocitric acid barium salt (100 µM, 1h) to inhibit astrocyte metabolism before recordings resulted in changes in excitability through altered membrane properties and ion channel function, at least in a subset of neurons, without significantly affecting synaptic responses at the PB-CeLC synapse. The data may suggest complex modulation of amygdala neuronal functions by astrocytes in neuropathic pain that include regulation of excitability, possibly as a compensatory or protective mechanism.

Disclosures: **M. Mazzitelli:** None. **V. Neugebauer:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.02/U5

Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS038261

Title: Bdnf in the amygdala modulates sensory and affective neuropathic pain behaviors

Authors: ***Z. J. HURTADO**, P. PRESTO, T. KIRITOSHI, G. JI, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Chronic pain is a profound and arduous health care issue to remediate. While many therapies are ineffective with adverse side effects, this requires a better mechanistic understanding to investigate new therapeutic strategies. It is well established now that the amygdala, a limbic brain region, plays a critical role in the modulation of pain, fear, and anxiety behaviors. Mechanisms of pain-related amygdala neuroplasticity are not fully understood. Previous data suggests that Brain Derived Neurotrophic Factor (BDNF) may be dysregulated in chronic pain models and neuropsychiatric diseases such as anxio-depressive disorders. BDNF given exogenously can ameliorate conditions like anxiety, pointing toward the amygdala as a potential target. However, the role of BDNF signaling in amygdala in pain modulation is not yet known. This study examined the effects of BDNF and a TrkB receptor antagonist (ANA-12) in the central amygdala on the modulation of pain and anxiety-related behaviors, using a chronic neuropathic pain model in rats (spinal nerve ligation, SNL). Adult male rats were implanted with a cannula targeting the central amygdala, and after 2 days of recovery, BDNF or ANA-12 were administered by micro-dialysis for 20 minutes. Sensory and emotional-affective behaviors were measured. BDNF, but not ANA-12, had antinociceptive effects in the von Frey test. BDNF, but not ANA-12, had anxiolytic effects on the Elevated Plus Maze. The data suggest that exogenous delivery of BDNF into the amygdala can modulate neuropathic pain behavior while the lack of clear antagonist effects suggest that this system is not activated in the pain condition.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.03/U6

Topic: D.02. Somatosensation – Pain

Support: USDA NIFA 2021-67017-3402

Title: Crosstalk between intestinal barrier, gut microbiota and amygdala neuropathology genes after ginger supplementation in female rats with neuropathic pain

Authors: *C.-L. SHEN[1], J. SANTOS[1], M. M. ELMASSRY[2], P. PRESTO[1], V. YAKHNITSA[1], N. ANTENUCCI[1], T. KIRITOSHI[1], G. JI[1], V. NEUGEBAUER[1];
[1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Princeton Univ., Princeton, NJ

Abstract: Objectives. The relationship between gut microbiota and neuropathic pain has received increasing attention. This study evaluated the effects of two dosages of gingerol-enriched ginger (GEG) on mechanical hypersensitivity, gut microbiome composition, intestinal permeability, and neuropathology signature genes expression in the amygdala of female rats in the spinal nerve ligation (SNL) model of neuropathic pain (NP). **Methods.** Forty female rats were divided into: Sham, SNL group, SNL+200mg GEG/kg BW, and SNL+600mg GEG/kg BW for 4 weeks. Emotional pain responses were assessed by vocalization test. Cecal samples were collected for microbiota composition analysis using 16S rRNA gene sequencing. Plasma lipopolysaccharide binding protein (LBP, a marker of intestinal permeability) levels were measured via ELISA. Neuropathology gene expression profiling of amygdala was conducted using the nCounter® Neuropathology pathway panel (NanoString Technologies, Seattle, WA). **Results.** Both GEG groups showed decreased vocalizations in the SNL model. G*ut microbiome diversity in both GEG groups was lower than in untreated SNL rats. SNL model induced the decrease of phyla, such as Bacteroidota,* Proteobacteria (e.g., *Sutterella stercoricanis*) and Firmicutes. Compared to untreated SNL group, both GEG groups had decreased abundance of *Rikenella*, Muribaculaceae, Clostridia UCG-014, *Mucispirillum schaedleri*, RF39, and Clostridia UCG-009 in feces. A few taxa showed a dose response with GEG treatments, such as RF39 and UCG-009, *Parasutterella*, *Hungatella*, and *Rikenella*. Both GEG groups had decreased levels of plasma LBP. Among the 770 genes, relative to sham rats, 1 gene (PLA2G4A) was upregulated and 2 genes (CDK5R1 and SHH) were downregulated in SNL rats. Compared to untreated SNL rats, GEG upregulated 9 genes (APC, CCNH, EFNA5, GRN, HEXB, ITPR1, PCSK2, TAF9 and WFS1) and downregulated 3 genes (AVP, C4A and TSPO) in the amygdala. **Conclusions.** GEG mitigates emotional pain responses in the female rats with NP, in part, via improved intestinal integrity and by reversing molecular neuroimmune signature of the amygdala. This was associated with changes in the gut microbiome composition which could play a role in mediating this phenotype. **Funding Sources.** USDA NIFA Grant no. 2021-67017-34026 (Shen/Neugebauer).

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.04/U7

Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS129552

Title: Sex differences in CGRP receptor-mediated synaptic plasticity in the amygdala in a mouse migraine pain model

Authors: *N. ANTENUCCI[1], V. YAKHNITSA[1], E. NAVRATILOVA[2], F. PORRECA[3], V. NEUGEBAUER[1];
[1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Pharmacol., [3]Dept Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Migraine is a debilitating neurological disorder with inadequate treatment options, emphasizing the need for a better understanding of its underlying mechanisms. Calcitonin gene-related peptide (CGRP) has been implicated in migraine pathophysiology, but a significant proportion of individuals do not respond to CGRP-targeted therapies that act outside the blood brain barrier. This study aimed to investigate central CGRP receptor-mediated mechanisms contributing to migraine pain and potential sex differences, using a mouse model. An important CGRP system in the brain is centered on parabrachial (PB) input to the amygdala known for its role in emotional processing and pain modulation, and CGRP receptors in the amygdala have been implicated in different pain conditions. The PB receives inputs from various pain-related pathways and other systems, including CGRP-containing trigeminal neurons. The PB relays these signals to multiple regions involved in pain perception and modulation, including the central nucleus of the amygdala (CeA). Here we explored the role of endogenous CGRP receptor activation at the PB-CeA synapse in a migraine model induced by dural application of CGRP, which induced facial allodynia in female but not male mice. Patch-clamp recordings of CeA neurons in brain slices from male and female mice 3 hours post dural CGRP showed that a CGRP receptor antagonist (CGRP 8-37) decreased excitatory transmission at the PB-CeA synapse more strongly in females compared to males, whereas effects on membrane properties were less clear. These observations suggest a potential sex-specific modulation of CGRP receptor-mediated synaptic plasticity in the context of dural CGRP-induced migraine pain. Sex differences in central CGRP system can contribute to the diverse manifestations and treatment responses observed in migraine patients.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: D.02. Somatosensation – Pain

Support: NIH grant NS038261
NIH grant NS106902
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NIH grant NS118731

Title: Region-specific photopharmacological modulation of mGlu5 receptor in a model of neuropathic pain

Authors: *V. NEUGEBAUER[1], S. NOTARTOMASO[2], F. LIBERATORE[2], N. ANTENUCCI[1], M. MAZZITELLI[1], G. BATTAGLIA[2], A. LLEBARIA[3], F. NICOLETTI[4];
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Abstract: The modulation of chronic pain by metabotropic glutamate receptor 5 (mGlu5) inhibitors has shown promising results in preclinical studies. However, the translation of these findings into successful clinical trials has been challenging, potentially due to region-specific opposing functions of mGlu5 receptors. To elucidate the underlying mechanisms and better understand these region-specific actions, we employed photopharmacology to selectively activate or inhibit mGlu5 receptors in distinct brain regions associated with pain processing, including the cingulate, prelimbic, and infralimbic cortices, thalamus, and amygdala. By using two different photoswitchable negative allosteric modulators (NAM) of mGlu5 receptors, we found that activating JF-NP-26 (a normally inactive, caged NAM) with blue-violet light in medial prefrontal cortical regions (infralimbic, prelimbic, anterior cingulate) and thalamus decreased hypersensitivity in the chronic constriction injury (CCI) mouse model of neuropathic pain. Systemically applied alloswitch-1 (a normally active NAM) produced similar antinociceptive effects that were reversed by silencing alloswitch-1 with blue-violet light and reinstated by green light. Surprisingly, local mGlu5 receptor activation in the amygdala had pronociceptive effects. To better understand the underlying mechanisms, we conducted whole-cell patch-clamp recordings on layer 5 pyramidal neurons in the prelimbic cortex, a region known to be involved in pain processing and modulation. Alloswitch-1 restored the excitatory drive onto prelimbic neurons, which could engage the descending pain modulatory system for the observed antinociceptive effects. Patch-clamp recordings of neurons in the laterocapsular division of the central nucleus of amygdala (CeLC), which receive inputs from the parabrachial nucleus and basolateral amygdala (BLA), a region implicated in emotional and pain processing, showed that alloswitch-1 decreased inhibitory postsynaptic currents at the BLA-CeLC synapse. These disinhibitory effects were reversed by blue-violet light-induced inactivation of alloswitch-1 and reinstated by green light. Our study provides valuable insights into region-specific actions of mGlu5 receptors in modulating chronic pain. Understanding mechanisms of region-specific differential functions of mGlu5 receptors may pave the way for the development of targeted therapies for chronic pain management.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.06/U9

Topic: D.02. Somatosensation – Pain

Support: NIH Grants NS038261
NS106902
NS109255

Title: Opposing effects of mu and kappa opioid receptors on amygdala output neurons in chronic neuropathic pain

Authors: *G. JI[1], E. NAVRATILOVA[2], F. PORRECA[2], V. NEUGEBAUER[1];
[1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Activation of opioid receptors has traditionally been assumed to produce analgesia. However, activation of mu opioid receptor (MOR) and kappa opioid receptor (KOR) in brain circuits appear to have opposing roles in pain. MOR and KOR are expressed in painassociated brain regions, including amygdala, which serves as the key brain region to modulate aversive responses to stress, fear, and pain. The relationship between synaptic plasticity in the amygdala and affective pain behaviors have been shown in animal pain models by our group and others. Multiple mechanisms have been identified, including enhanced excitatory neurotransmission at the parabrachial (PB)-central amygdala (CeA) synapses, increased excitability of the CeA neurons, and increased activity of CeA output neurons to amplify pain responses in chronic pain states. Studies in animal pain models demonstrated analgesic effects of MOR activation in the CeA. In contrast, blockade of dynorphin/KOR signaling in the right CeA with microinjection of nor-BNI prevented pain- and stress-induced allodynia. Thus, MOR and KOR in the CeA may have opposing effects in pain. In this study, we performed brain slice physiology experiments to test the effects of a MOR agonist (DAMGO) and KOR antagonist (nor-BNI) on neurons in the lateral CeA (CeL) in brain slices from neuropathic mice (SNL model). DAMGO significantly decreased frequency, but not amplitude, of spontaneous excitatory postsynaptic currents (sEPSCs) and also excitability of CeL neurons in brain slices from SNL mice. DAMGO had no effect on frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) in CeL neurons. Nor-BNI significantly increased frequency, but not amplitude, of sIPSCs and also excitability of CeL neurons in brain slices from SNL mice. Nor-BNI had no effect on frequency and amplitude of sEPSCs in CeL neurons in brain slices from SNL mice. The data suggest that MOR and KOR circuits differentially involve excitatory and inhibitory pathways modulating CeA outputs. Simultaneous targeting of these opposing MOR/KOR mechanisms may provide an optimal therapeutic strategy to treat chronic pain.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS038261
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NIH Grant NS120395

Title: Kappa opioid receptor signaling in hypothalamus promotes stress-induced functional pain

Authors: *V. YAKHNITSA[1], N. ANTENUCCI[1], B. MENDOZA[1], E. NAVRATILOVA[2], F. PORRECA[2], V. NEUGEBAUER[1];
[1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Univ. of Arizona Col. of Med., Univ. of Arizona, Tucson, AZ

Abstract: More than 15% of the population worldwide suffers from chronic pain in the absence of identifiable tissue injury. Examples of such functional pain syndromes (FPS) include fibromyalgia, migraine, and irritable bowel syndrome. Most of FPS are female-prevalent. FPS patients experience pain-free interictal periods interrupted by attacks of pain (ictal periods). Human imaging studies demonstrated that the hypothalamus is activated prior to the ictal phase. Stress, a key trigger of the ictal phase of FPS, promotes the release of hypothalamic dynorphin, an endogenous kappa opioid receptor (KOR) agonist. Systemic dynorphin, or stress, increases pituitary hormone prolactin (PRL) predominantly in females. Tuberoinfundibular dopamine (TIDA) neurons in the hypothalamic arcuate nucleus (Arc) provide tonic inhibition of PRL release from pituitary lactotrophs. In this project we test the novel hypothesis that repeated stress potentiates KOR signaling in the hypothalamus resulting in increased release of PRL that produces FPS-like pain selectively in females. The functional pain model was induced in female KOR-CRE mice using a repeated restrained stress (RRS) paradigm. After assessment of mechanosensitivity to von Frey filaments and anxiety-like behaviors in the elevated plus maze test, brain slice physiology experiments were performed in two groups: stressed group (3 days after stress) and stress-resolved group (14 days post stress). Whole-cell patch-clamp recordings were made from KOR-positive Arc-TIDA neurons in the right hypothalamus. KOR-positive cells were labeled with inhibitory DREADD (AAV5-hSyn-DIO-hM4D Gi) 3 weeks before slice preparation. Dopamine-containing neurons were labeled by i.v. injection of fluorogold (2%, 30-40 µl) 1 week before recordings. RRS priming induced long-lasting (up to 12 days) allodynia and anxiety-like behaviors in mice. Three neuronal phenotypes were observed in both stressed and stress-resolved groups: spontaneous bursting, regular firing, and silent neurons. In the stressed group, superfusion of a KOR agonist (U69, 593) suppressed firing in bursting and regular firing neurons more strongly than in stress-resolved mice. U69, 593 reduced excitability of all neuronal phenotypes in both animal groups. These results suggest that stress enhances

hypothalamic KOR signaling that modulates activity of Arc-TIDA neurons promoting FPS-like pain. The results advance our knowledge on mechanisms of FPS and help develop strategies to prevent chronification of pain.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.08/V1

Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS038261
NIH Grant NS118731

Title: Pain-related synaptic and excitability changes in PB- and PAG-projecting amygdala CRF neurons in a neuropathic pain model

Authors: *T. KIRITOSHI, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The central nucleus of the amygdala (CeA) plays a key role in pain modulation and pain-related emotional-affective aspects of pain. The CeA contains a high level of corticotropin releasing factor (CRF)-expressing neurons that project to a wide range of brain areas including key pain modulatory regions in the brainstem such as the parabrachial area (PB) and periaqueductal gray (PAG). Our recent study revealed that manipulation of CeA-CRF neurons can modulate neuronal activity in the spinal cord and pain-related behaviors. However, functional differences as well as pain-related cellular and synaptic changes in projection-defined CeA-CRF neurons remain to be determined. Here we sought to determine any differences between PB- and PAG-projecting CeA-CRF neurons under baseline conditions and in a neuropathic pain model using cell-type specific retrograde labelling and slice patch-clamp recording. Retrograde Cre-dependent adeno-associated viral vectors AAVrg-hSyn-DIO-EGFP and AAVrg-FLEX-tdTomato were stereotaxically injected into the PB and PAG, respectively, of transgenic Crh-Cre rats to identify PB- and PAG-projecting CeA-CRF neurons in brain slices. Whole-cell patch clamp recordings were obtained from retrogradely labeled CeA-CRF neurons in brain slices from naïve, sham control, and neuropathic rats (1 week after L5 spinal nerve ligation, SNL model). In current clamp mode, neuronal excitability was measured by injecting depolarizing currents. In voltage clamp mode, excitatory postsynaptic currents (EPSCs) were evoked by electrical stimulation of presumed PB input. In addition, we conducted immunohistochemistry (IHC) to determine colocalization of these projection neurons with other neurochemical markers such as somatostatin (SOM) and protein kinase C delta (PKCδ). PB- and PAG-projecting CRF neurons are largely non-overlapping populations, and PB-projecting CeA-

CRF neurons showed slightly higher excitability than PAG-projecting CeA-CRF neurons under baseline conditions. We found increased excitability in PAG-projecting, but not PB-projecting, CeA-CRF neurons in the SNL model compared to sham control. We also found enhanced EPSCs in both projection neurons but the enhancement was greater in PAG-projecting CeA-CRF neurons. Our IHC data suggest that subsets of PB- and PAG-projecting neurons colocalize with SOM but very rarely colocalize with PKCδ. These results suggest that CeA-CRF neurons undergo differential changes in pain conditions depending on their projection targets.

Disclosures: T. Kiritoshi: None. **V. Neugebauer:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.09/V2

Topic: D.02. Somatosensation – Pain

Support: NIH Grant NS038261

Title: Cell type-specific transcriptomic profile of the central amygdala in rat model of chronic neuropathic pain

Authors: *P. PRESTO, M. MCMANUS, I. PONOMAREV, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Chronic pain is a pervasive and complex healthcare issue, presenting a challenge to the identification of effective therapeutic strategies. Successful treatment options are hindered due to a lack of full understanding of the mechanisms and targets involved in the transition to a chronic pain state. Therefore, mechanistic insights into pain-related signaling processes are critical to identify new molecular targets for pain relief. Abnormal changes in gene expression may ultimately impact disease states. Transcriptomic analysis provides crucial insight into mRNA transcripts from cells in various conditions, rendering this method an appealing approach to the discovery of novel molecular targets. Transcriptomic profiling in the periphery and spinal cord has revealed an upregulation of many transcription factors and cytokines in neuropathic pain, though pain-related gene expression profiles within the brain are understudied. A limbic brain region, the amygdala is a key player in the emotional-affective aspects of pain and pain modulation. Changes in amygdala activity have been observed in pain models and neuroplasticity within the amygdala has been linked to pain-related behaviors. However, the molecular signatures of pain-related amygdala plasticity that may drive these behaviors remain to be determined. Here we characterize the amygdala transcriptional profile of adult male and female rats at the acute (1 week) and chronic (4 week) stages of neuropathic pain. Central nucleus of the amygdala (CeA) tissues were collected for single nuclei RNA sequencing after spinal nerve ligation (SNL) or sham surgery. After filtering using the 10X Genomics Cell Ranger analysis pipeline, a total of 29,840 nuclei were identified, with 23 discrete graph-based clusters

corresponding to specific cell types. As increasing evidence has implicated a role of neuroimmune signaling in chronic pain pathogenesis, a particular focus was on differentially expressed genes (DEGs) in non-neuronal cells such as microglia and astrocytes. Two distinct microglial subpopulations were identified, with 87 and 101 DEGs in each subcluster. Likewise, two astrocytic subgroups containing 43 and 118 DEGs were identified. Cell type-specific DEGs included *Sall1* and *C1qa* in microglia and *Gja1* and *S100b* in astrocytes from SNL rats, suggesting that neuropathic pain may trigger expression of transcriptional regulators that have previously been implicated in neuroinflammation, neurodegeneration, and impaired cognition. The results suggest heterogeneity of gene expression responses in neuroimmune cell types in pain, providing mechanistic insight into pain-related amygdala function.

Disclosures: **P. Presto:** None. **M. McManus:** None. **I. Ponomarev:** None. **V. Neugebauer:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.10/V3

Topic: D.02. Somatosensation – Pain

Support: NS038261

Title: Effects of innate immune activation in the rat right and left central amygdala on pain-like behaviors

Authors: *I. PONOMAREV[1,2], P. PRESTO[1,2], M. MAZZITELLI[1,2], B. LIU[1,2], V. NEUGEBAUER[1,2];
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Abstract: Chronic pain is a pervasive global healthcare issue affecting millions of individuals every year. Mechanistic knowledge of pain-related signaling processes in the brain is a prominent knowledge gap. Increasing evidence has demonstrated a role for neuroimmune signaling factors in the pathogenesis of chronic pain. Within the brain, the amygdala, a bilateral limbic structure, is involved in the emotional-affective dimensions of pain. Preliminary evidence has suggested pain-related right-hemispheric lateralization in the central nucleus of the amygdala (CeA) in different pain models. Whereas a pro-nociceptive phenotype has been characterized in the right CeA, the left CeA may have an anti-nociceptive influence on pain modulation. However, little has been explored regarding pain-related lateralization of neuroimmune signaling mechanisms in the CeA following exogenous stimulation. This study examined the effects of exogenously-induced activation of the innate immune system, localized either to the right or left CeA, on pain-related behaviors. Two potent immunostimulants - lipopolysaccharide (LPS), a component of gram-negative bacteria and toll-like receptor 4 (TLR4) agonist; or polyinosinic-polycytidilic acid (poly I:C), a known viral mimetic and TLR3 agonist - were used to probe this

neuroinflammatory state compared to vehicle control (artificial cerebrospinal fluid, ACSF). LPS, poly I:C, or ACSF was stereotaxically delivered directly into either the left or right CeA of male and female rats. Three or 7 days post drug delivery, sensory thresholds (von Frey test) and emotional-affective responses (vocalizations in response to a noxious stimulus) were measured. Intra-CeA injections of LPS but not poly I:C produced an increase in mechanosensitivity compared to ACSF in both sexes at both time points, regardless of hemisphere. At the 3-day time point, LPS but not poly I:C produced an increase in ultrasonic vocalizations in both sexes and both hemispheres; however, at the 7-day time point, both LPS and poly I:C produced an increase in ultrasonic vocalizations that was specific to the right CeA. The results suggest that both right and left CeA are capable of generating sensory and emotional pain-like behaviors when activated exogenously via TLR4-mediated neuroimmune signaling, but emotional-affective responses induced via TLR3-based neuroimmune activation at a later stage are lateralized to the right hemisphere. Further mechanistic insight into the functional lateralization of pain processing in the amygdala will aid the development of therapeutic strategies for chronic neuropathic pain relief.

Disclosures: I. Ponomarev: None. **P. Presto:** None. **M. Mazzitelli:** None. **B. Liu:** None. **V. Neugebauer:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.11/V4

Topic: D.02. Somatosensation – Pain

Title: Time-dependent contribution of the PbN to CeA pathway to pain-related behaviors in mouse models of persistent pain

Authors: *T. D. WILSON[1], J. TORRES-RODRIGUEZ[2], S. SINGH[2], S. CHAUDHRY[2], A. ADKE[2], J. BECKER[2], J. LIN[2], S. MARTINEZ GONZALEZ[2], S. VALDIVIA[2], O. SOLER-CEDEÑO[2], Y. CARRASQUILLO[1];
[1]NIH, Bethesda, MD; [2]NCCIH/NIH, Bethesda, MD

Abstract: The parabrachial nucleus (PbN) is an important brain region carrying nociceptive information from the spinal cord to the brain. The central amygdala (CeA), a structure that modulates emotional behavior and pain, is one of the main targets of the PbN. Studies have further shown potentiation of synaptic transmission in the PbN→CeA pathway after injury in different rodent pain models. Additional studies demonstrated that this pathway contributes to escape and aversion behaviors. However, the function of the PbN→CeA pathway in injury-induced pain-related behaviors remains unknown. Our goal was to address this question using optogenetic assisted circuit mapping, histology, and a chemogenetic intersectional approach in mouse models of persistent pain. This experimental design allowed us to target and modulate the activity of CeA-projecting PbN neurons in animals with persistent pain. Slice

electrophysiological experiments showed that PbN inputs to the CeA are independent of CeA genetic identity or firing type. Histological analysis further showed robust expression of the neuronal activity marker, Fos, in the PbN after peripheral noxious stimuli. Using a battery of behavioral tests and intersectional chemogenetic manipulations, we also showed that CeA-projecting PbN neurons were necessary for injury-induced behavioral hypersensitivity in all modalities tested as well as for spontaneous licking responses to formalin paw injection without affecting baseline nociception. Notably, our experiments showed that the contribution of this pathway to injury-induced hypersensitivity was time-dependent, contributing to injury-induced hypersensitivity 1w, but not 3w, after injury. Parallel chemogenetic activation experiments further showed that CeA-projecting PbN neurons were sufficient to cause modality-specific hypersensitivity without injury. Additional pilot experiments showed that continuous chemogenetic activation of CeA neurons expressing protein kinase C delta or the calcitonin gene-related peptide receptor for 2wks resulted in prolonged hypersensitivity that outlasted chemogenetic activation and returned to baseline 7d after termination of chemogenetic treatment. Collectively, our results show that the PbN→CeA pathway contributes to pain-related behaviors following injury without affecting baseline nociception. Our results showing that pain modulation by this pathway is time-dependent provide insights about mechanisms driving the transition from acute to chronic pain. Current experiments are evaluating whether the contribution of genetically distinct CeA cell types to pain modulation is also time-dependent.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.12/V5

Topic: D.02. Somatosensation – Pain

Title: Electrophysiological properties of distinct neuronal populations in the spinopontoamygdaloid pathway in a mouse model of neuropathic pain

Authors: B. NEUGEBAUER[1], M. L. TORRUELLA-SUAREZ[2], S. CHAUDHRY[2], T. D. WILSON[2], S. SINGH[2], J. L. LIN[2], *Y. CARRASQUILLO[3];
[1]NIH, NCCIH, Bethesda, MD; [3]NCCIH, [2]NIH, Bethesda, MD

Abstract: The spinopontoamygdaloid pathway relays nociceptive information from the spinal and medullary dorsal horns to the parabrachial nucleus (PBN), which then projects to the central amygdala (CeA). Pain-related synaptic plasticity in this pathway has been extensively characterized in rodent models of persistent pain. Within the CeA, intrinsic and firing properties are cell-type-specific, with neurons expressing somatostatin (Som+) showing greater excitability than those expressing protein kinase delta (PKCδ+). After injury, PKCδ+ and Som+ neurons

show opposing functions in pain-related behaviors and display opposing changes in excitability. Whether pain-related excitability changes in PBN and other genetically distinct CeA neurons occur following injury remains unknown. We addressed this question by examining the properties of projection-specific and genetically distinct neurons within this pathway using a mouse neuropathic pain model and ex-vivo patch-clamp electrophysiology in acute PBN and CeA slices. In the PBN, we saw heterogenous firing types in both pain and control conditions. In addition, we saw an increased number of spontaneously firing PBN neurons and increases in evoked firing after nerve injury. In contrast, regular spiking PBN neurons show decreased excitability in response to nerve injury compared to control conditions. We did not see measurable injury-induced changes in the intrinsic membrane properties measured, suggesting that these phenotypes are extrinsically mediated. Recordings from CeA-projecting PBN neurons further showed that intrinsic membrane and firing properties were unaltered by nerve injury, indicating that injury-induced changes are projection-specific. At the CeA level, we saw sexual dimorphism in both electrophysiological properties and behavioral function of PKCδ+ neurons 1w following injury. Recordings in cells expressing calcitonin gene-related peptide receptor (CGRPR+) neurons further showed that excitability is dependent on the rostro-caudal level, with greater excitability observed in posterior CGRPR+ cells, compared to anterior cells, in both nerve injury and control conditions independently of sex. After injury, we saw increases in the excitability of CGRPR+ cells in posterior, but not anterior CeA. Notably, we do not see changes in the excitability of PKCδ+ and CGRPR+ neurons 4w after injury, when animals still display pain-related behavioral hypersensitivity. Together, our findings revealed that pain-related changes in the firing properties of PBN and CeA neurons are complex and depend on firing type, projection, genetic identity, sex, anatomical location, and time after injury.

Disclosures: B. Neugebauer: None. **M.L. Torruella-Suarez:** None. **S. Chaudhry:** None. **T.D. Wilson:** None. **S. Singh:** None. **J.L. Lin:** None. **Y. Carrasquillo:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.13/V6

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DK128475

Title: Identification of spinal cord neurons involved in the modulation of interstitial cystitis and bladder pain

Authors: *Y. ZHANG, F. LIU, H. HAHM, M. HEITMEIER, V. SAMINENI;
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Abstract: Interstitial cystitis and bladder pain (IC/BPS) are chronic conditions that affect 8 million women in the United States. Despite this knowledge, our understanding of spinal

mechanisms that are engaged in the IC processing is largely unknown. Here we took an unbiased approach using immediate early gene (cFos) mapping for precise dissection of brain circuits that mediate IC/BPS. These studies identified the small group of neurons in the spinal cord that are critical for IC/BPS. We manipulated the activity of these spinal neurons using chemogenetics and ablation approaches to study the role of these neurons in IC/BPS. Engineered excitatory (Gq) or inhibitory (Gi) GPCRs (DREADDs) or Casp3 were expressed in functionally-defined spinal neurons via adeno-associated viral vectors. Selective activation of these neurons can attenuate evoked bladder pain and silencing these neurons could elicit visceral hypersensitivity. Taken together, these findings reveal unique sacral spinal cord neurons play a significant role in modulating the bladder pain, which provide a valuable hint for understanding information processing in the pelvic pain.

Disclosures: Y. zhang: None. **F. Liu:** None. **H. Hahm:** None. **M. Heitmeier:** None. **V. Samineni:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.14/V7

Topic: D.02. Somatosensation – Pain

Support: NIH grant DK128475

Title: A highly scalable retrograde AAV approach for multiplexed visualization and simultaneous single-cell profiling of neuronal projections

Authors: *L. YANG[1,2], F. LIU[1], H. HAHM[1], T. OKUDA[1], Y. ZHANG[1], V. KALYANARAMAN[1], M. HEITMEIER[1], V. SAMINENI[1];
[1]Dept. of Anesthesiol., [2]PhD Program in Neurosciences, Washington Univ. in St. Louis, St. Louis, MO

Abstract: Motor and sensory cortex send axonal projections to numerous brain regions and their recruitment has been shown to modulate pain sensation. However, with the current labeling strategy using retrograde fluorophores, the number of projection targets that can be examined in a single experiment is limited (up to five for most laboratory settings). Here we develop STL-PUB (study of long-range projections using RNA barcodes), a scalable and powerful platform that labels distinct projections using retrograde adeno-associated viruses expressing unique RNA barcodes. We utilized STL-PUB to label seven parallel projection targets of the motor and sensory cortex in individual mice. By profiling the primary somatosensory region and the primary motor region of the cortex using single-nucleus RNA sequencing, we were able to map the seven projection targets to distinct cortical neuron cell types at single-cell level. Furthermore, we examined the cortical projections that are preferentially activated in a mouse model of visceral pain by quantifying the projection targets in neurons that induce the expression of

immediate early genes, as markers for increased neuronal activity. In summary, we demonstrated that STL-PUB enables systematic profiling of the projections of brain regions and applied it to understand the cell types and projection targets in the mouse cortex that are activated by visceral pain.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.15/V8

Topic:

Support: NIH Grant DK128475

Title: Physiological characteristics of the sacral spinal cord projecting RVM neurons

Authors: *T. OKUDA[1], F. LIU[2], V. K. SAMINENI[2];
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Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating condition characterized by severe bladder pain and loss of bladder control. Understanding the neuronal mechanisms involved in bladder pain modulation is crucial for developing effective treatments. The rostro ventromedial medulla (RVM) has been implicated in the descending modulation of pain, including sensory signals related to the bladder at the spinal cord level. However, the specific characteristics of RVM neurons projecting to the sacral spinal cord (SSCprj) remain poorly defined. In this study, we employed AAV tracing and patch-clamp techniques to investigate the properties of SSCprj RVM neurons. Using slice electrophysiology experiments, we found that the majority of SSCprj RVM neurons exhibited a "Regular Spiking" pattern. Interestingly, most SSCprj RVM neurons did not express either mu-opioid receptors (MOR) or kappa-opioid receptors (KOR), suggesting the existence of a distinct subpopulation of "Neutral cells" that deviate from the classical ON or OFF cell categories. Furthermore, we examined altered synaptic inputs to SSCprj RVM neurons in a mouse model of bladder pain. Our findings revealed significant changes in synaptic activity, indicating the potential involvement of SSCprj RVM neurons in the development of bladder pain associated with cystitis. Overall, these results provide novel insights into the characteristics of SSCprj RVM neurons in the context of cystitis, shedding light on how altered activity in these neurons contributes to the development of bladder pain.

Disclosures: T. Okuda: None. **F. Liu:** None. **V.K. Samineni:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.16/V9

Topic: D.02. Somatosensation – Pain

Title: An exploratory study of the anti-nociceptive effect of electroconvulsive stimulation in rats

Authors: *J. TREJO, Z. WANG, P. N. FUCHS, Y. B. PENG;
Univ. of Texas, Arlington, Arlington, TX

Abstract: The implementation of electroconvulsive therapy (ECT) has long been utilized for many decades. More specifically, the shock stimulation of ECT has been mostly used with major depressive patients who have revealed resistance to other modes of treatment and has also been used in patients with chronic pain. The local field potential (LFP) is a powerful electrophysiological tool that records the summation of electrical activity around the tip of an electrode. The LFP can be subdivided into five frequency bands: delta (0.1 - 3 Hz), theta (3 - 7 Hz), alpha (7 - 12 Hz), beta (12 - 30 Hz), and gamma (30 - 100 Hz), and their power is used to reflect the change of specific brain activities. In the present study, to explore how ECT is effective in relieving pain, we recorded continuous LFP in four distinct regions of the male adult Sprague-Dawley rat brain from intracranially implanted electrodes: right anterior cingulate cortex (ACC), bilateral amygdala (AMG), and the right ventral tegmental area (VTA). Under isoflurane anesthesia, the LFP was recorded in 3 separate 3% formalin-induced nociceptive conditions: formalin-only (control condition), ECT post-formalin, and ECT pre-formalin. The multi-ECT shock remained consistent in both ECT experimental conditions with 3 separate parameters of 50pulse/s, 0.7ms, 2s at 5mA, 20mA, and 50mA delivered 3 times, 10-15s apart. By using power spectrum analysis, the results of this study revealed a mixed effect. Some animals displayed an ECT-induced inhibitory effect in LFP power, while others showed excitation or no LFP change. The change of LFP power also varies among the four distinct locations, even within the same rat. Furthermore, either the ECT-induced increase or decrease of power has a duration of a few seconds to a few minutes, which is not what we originally expected as a long-lasting effect. It is possible that the sensitivity to isoflurane that determines the depth of anesthesia may play a role in causing this variability. Further behavioral research in combination with ECT and LFP in freely-moving animals is required to determine the underlying neural mechanism of the ECT anti-nociceptive effect.

Disclosures: **J. Trejo:** None. **Z. Wang:** None. **P.N. Fuchs:** None. **Y.B. Peng:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.17/V10

Topic: D.02. Somatosensation – Pain

Support: CIHR Grant

Title: Investigating the role of the ventral anterior cingulate cortex in placebo analgesia

Authors: *S. K. REHAL[1], C. CHO[2], L. J. MARTIN[1];
[1]Cells & Systems Biol., Univ. of Toronto, Mississauga, Mississauga, ON, Canada; [2]Psychology, Univ. of Toronto, Mississauga, ON, Canada

Abstract: Chronic pain is one of the largest health epidemics, affecting ~20% of the population worldwide and costing over $685 billion per year in medical expenses and lost work productivity. The persistence of pain after an injury has healed is thought to result from maladaptive learning such that systems initially involved in tissue recovery and survival have gone off course and become dysfunctional. However, this learning may be malleable and reversible through pharmacological conditioning, where the administration of analgesic drugs becomes associated with specific contextual cues. In this phenomenon, the mere pairing of drugs with environmental or situational stimuli can trigger pain relief in the absence of active drug. This concept is commonly referred to as placebo analgesia. In the current study, we used the spared nerve injury (SNI) model of chronic pain combined with a regimen of morphine treatment whereby we administered morphine over four days within specific contextual chambers. Following morphine conditioning, mice were injected with a saline solution on a test day, which resulted in robust analgesia. Whole brain c-fos analysis was conducted and the ventral anterior cingulate cortex (vACC) was identified as a candidate region driving conditioned morphine analgesia. Next, we investigated the role of the vACC and mu-opioid receptors within this region to determine whether they are specifically required for conditioned morphine analgesia. Our results indicate that when the vACC is stimulated on test day, the placebo analgesic response is abolished. Furthermore, results indicate that mu-opioid receptor activation in the vACC was required for placebo analgesia. This data furthers our understanding of the role of the vACC in placebo analgesia and contributes to the advancement of intervention and treatment strategies for individuals suffering from chronic pain. Specifically, these findings suggest that contextual cues, such as the expectation of pain relief, may play a greater role in pain management than initially thought.

Disclosures: S.K. Rehal: None. **C. Cho:** None. **L.J. Martin:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.18/Web Only

Topic: D.02. Somatosensation – Pain

Title: Oxytocinergic projection of the paraventricular nucleus hypothalamic to the trigeminocervical complex

Authors: *S. FLORES BOJORQUEZ[1], M. CONDÉS LARA[2], A. GONZALEZ-HERNANDEZ[1], G. MARTÍNEZ LORENZANA[2];
[1]Inst. De Neurobiología, UNAM, Queretaro, Mexico; [2]Univ. Nacional Autónoma De México, Queretaro, Mexico

Abstract: The Trigemino Cervical Complex (TCC) plays a fundamental role in the modulation of nociception ofcraniofacial structures. Studies in our laboratory have shown that the descending oxytocinergic (OT)pathway of the Hypothalamic Paraventricular Nucleus (NPV) participates in the production ofanalgesia and anti-nociceptive processes that take place in the segment lumbar spinal cord.However, the OT projection to the Trigeminal Cervical Complex has not been studied; Therefore, thiswork aimed to analyze the projection of the NPV to the TCC by neural tracing anterograde andimmunofluorescence to OT. This study was conducted in male rats of the Wistar strain that werestereotaxically injected with the Fluro Ruby (FR) or Biotin Dextran Amine (BDA) antegrade tracers inthe NPV; after 10 days obtained, the brain and TCC. Coronal, sagittal, or horizontal as the case maybe, to which the technique of immunofluorescence to OT. The TCC is divided into the most caudalregion of the nucleus spinal trigeminal caudalis (Sp5C) and in the upper cervical segments (C1-C2).The results were: a scarce distribution of the NPV projection with FR or BDA at the level of Sp5C anddenser in C1-C2 at the level dorsal; also, fibers that colocalize and not between OT and FR wereobserved. The morphological results obtained in this work support recent electrophysiologicalstudies in our laboratory, which indicate that the electrical stimulation of the NPV generates a blockof information entry nociceptive at the TCC level. We acknowledge Eng. Elsa Nydia Hernández Ríosfor her technical assistance with the confocal microscope.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.19/V12

Topic: D.02. Somatosensation – Pain

Support: NIH-NIA RO1 AG073126
NIH-NIDCR R21 DE027808

Title: Sex differences in diffuse noxious inhibitory control are mediated by the rostral anterior cingulate cortex periaqueductal gray circuit

Authors: *I. CORREIA ROCHA[1], R. SANTO[2], Y. ZHANG[2], J. DA SILVA[2], J. RO[2];
[1]Univ. of Maryland - Baltimore, Baltimore, MD; [2]Dept. of Neural and Pain Sciences, Ctr. to Advanced Chronic Pain Res., Univ. of Maryland, Baltimore, MD

Abstract: Conditioned pain modulation (CPM), often described as diffuse noxious inhibitory control (DNIC) in preclinical settings, is widely used as an index of endogenous pain inhibitory function. CPM is also more efficient in healthy men than women, and a reduced level of CPM is observed in female-predominant disease conditions. However, the neurobiological mechanisms underlying sex differences in CPM are relatively unknown. Previously, we demonstrated that DNIC is stronger in male rats compared to female rats, and the efficient DNIC in males is associated with a stronger functional connectivity between rACC and PAG. In this study, we investigated the nature of interactions between rACC and PAG in the context of our DNIC paradigm. First, we examined whether rACC is a critical brain region for mediating DNIC by inactivating rACC with lidocaine. The temporary inactivation of rACC in males led to a DNIC response similar to that observed in females. We then investigated whether the DNIC responses we observed involved endogenous opioid mechanisms. Systemic treatment with naloxone significantly attenuated the DNIC response in males and eliminated sex differences. To investigate whether PAG plays a role in mediating endogenous opioid effects, we microinjected naloxone directly into PAG of males. Consistent with our prediction, this treatment significantly attenuated the DNIC response in males. Moreover, microinjection of morphine directly into the PAG of females significantly enhanced the DNIC response to an extent similar to that observed in males. Additionally, we conducted a preliminary chemogenetic experiment in which we selectively inhibited rACC neurons projecting to PAG in male rats. DNIC responses in males transfected with DREADDi were significantly blunted. Collectively, these results support our hypothesis that the difference in the strength of functional connectivity between the rACC to PAG mediates sex differences in DNIC efficiency, and that strong rACC to PAG connectivity, involving opioid processing in PAG, is required for efficient DNIC.

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Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

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Program #/Poster #: PSTR081.20/V13

Topic: D.02. Somatosensation – Pain

Support: ERC Grant

Title: Rostral ventromedial medulla neurons mediate sleep deprivation-induced pain sensitivity

Authors: *M. ALTINKÖK, M. FATT, P. ERNFORS;
Med. Biochemicstry and Biophysics, Karolinska Inst., Stockholm, Sweden

Abstract: Sleep disorders are known risk factors for chronic pain diseases, and recent studies have indicated the role of sleep deprivation on pain modulation. The descending pathway in the nervous system is involved during the psychological processing of pain, and recent findings suggest its potential role during sleep deprivation-induced pain modulation. However, little is known about the molecular and cellular mechanisms in the descending pathway that are engaged in order to modulate pain perception upon sleep deprivation. Here, we investigated the role of the Rostral Ventromedial Medulla (RVM) neurons in pain modulation upon sleep deprivation in mice. By performing single nuclei RNA sequencing (snRNAseq) and chemogenetic manipulations of the RVM neurons, we show the sufficiency of the RVM neurons during sleep deprivation-induced pain sensitivity. We report that the chemogenetic stimulation of the sleep deprivation-activated RVM neurons results in a significant increase in pain sensitization. Chemogenetic inhibition of sleep deprivation activated RVM neurons appear to increase the mechanical pain threshods. Together, our study indicates the RVM as a key region in sleep deprivation-induced pain sensitivity, and highlights the potential role of the descending pathway in co-morbid sleep and chronic pain disorders.

Disclosures: **M. Altinkök:** A. Employment/Salary (full or part-time):; Karolinska Institutet. **M. Fatt:** A. Employment/Salary (full or part-time):; Karolinska Institutet. **P. Ernfors:** A. Employment/Salary (full or part-time):; Karolinska Institutet.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.21/V14

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DE029946, DE029187, NS091296, DE 02773

Title: Active ACC-RVM neuronal circuit maintains 5-HT-dependent descending pain facilitation after nerve injury

Authors: J. YANG, C. BIAN, W. GUO, S. ZOU, K. REN, *F. WEI;
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Abstract: The rostral ventromedial medulla (RVM) relays input from the periaqueductal gray (PAG) to the spinal dorsal cord and has been considered pivotal in descending pain modulation. Recent evidence indicates that 5-HT-dependent descending facilitation from the RVM plays a critical role in the development of persistent pain in animal models. Although the PAG receives input from affective pain-related cortical structures including the anterior cingulate cortex (ACC), stimulation of the PAG-RVM circuit produces opioid-dependent pain inhibition, suggesting this classic circuit may not mediate ACC-involved pain facilitation. The hyperexcitability of both pyramidal ACC neurons and 5-HT RVM neurons are involved in the

development of persistent pain. However, it is still unclear whether 5-HT-dependent descending facilitation is derived from ACC input. To examine whether ACC-RVM circuit exists, we performed neuronal tracings and confirmed a direct and unidirectional ACC-RVM pathway in the mice. To explore the function of the ACC-RVM circuit in nociception, we employed a two-step viral infection with Cre and ChR2 as well as excitatory optogenetic manipulation to selectively target and activate RVM-projecting pyramidal neurons in the ACC or their terminals in the RVM. The effects of the activation of RVM-projecting ACC neurons on neuronal and glial activity in the RVM were examined. We observed c-Fos and pERK expression in many RVM neurons and reactivation of local microglia and astrocytes. Consistently, selective activation of ACC-RVM results in behavioral hyperalgesia/allodynia and aversive responses in normal mice, which could be blocked by intra-RVM lidocaine treatment or significantly attenuated by intra-RVM Tph2-shRNA pretreatment, supporting that descending outflow from RVM neurons including 5-HT neurons mediates endogenous cortical pain facilitation, which may be implicated in the development of functional or central pain conditions without tissue and nerve injury. We further examined whether inhibiting the ACC-RVM pathway could reduce the induction and maintenance of hyperalgesia in the CCI-ION model. After the eNpHR channel was selectively expressed in RVM-projecting ACC neurons, we found that optogenetic inhibition obviously suppressed behavioral hyperalgesia and aversive responses at 1 and 4 w after CCI. Together, these findings indicate that the RVM directly receives excitatory input from the ACC, and suggest that the hyperactive ACC-RVM pathway is involved in the upstream mechanisms of 5-HT-dependent descending facilitation underlying the persistence of neuropathic pain or the development of central pain conditions.

Disclosures: **J. Yang:** None. **C. Bian:** None. **W. Guo:** None. **S. Zou:** None. **K. Ren:** None. **F. Wei:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.22/V15

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DE029946
NIH Grant DE029187

Title: Cd200 receptor signaling in the rostral ventromedial medulla contributes to homeostatic descending pain modulation

Authors: W. GUO, J. YANG, C. BIAN, S. ZOU, F. WEI, *K. REN;
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Abstract: CNS homeostasis is maintained by multiple inhibitory signaling pathways, among which the CD200-CD200 receptor (R) signaling supports an anti-inflammatory phenotype of

microglia. CD200 is a glycoprotein distributed in neurons including excitatory synapses and acts selectively through inhibitory CD200R on microglia to regulate neuroimmune interaction. We studied the role of CD200 in the RVM (Rostral Ventromedial Medulla), a key region of descending pain modulation, in the maintenance of neuropathic pain in a mouse model with chronic constriction injury of the infraorbital nerve (CCI-ION). Immunostaining staining showed that numerous Neu-N and vGluT2-labeled cells in the RVM exhibit CD200, suggesting that CD200-expressing cells are excitatory neurons. Meanwhile, only Iba1-positive microglia expressed CD200R and were closed to CD200-labeled neurons, supporting the presence of the CD200-CD200R signaling for neuron-microglia interactions. In naive mice, RNAi of CD200R in the RVM led to behavioral nociceptive hypersensitivity at 8d and 28d, as indicated by an increase in mechanical and thermal sensitivity. The injection of anti-CD200R antibodies into the RVM also facilitated nociception. Thus, CD200-CD200R signaling is inhibitory and helps to maintain behavioral nociception. Next, we found that both CD200 and CD200R1 were downregulated in the RVM after CCI-ION, along with increased proinflammatory IL-1beta and reduced anti-inflammatory IL-10 expression. These results indicate that pro-inflammatory signaling is predominant and outweighs the anti-inflammatory limb of immune response after injury. To verify whether reduced expression of CD200R in the RVM contributes to neuropathic pain, we employed CRISPR/Cas9 Synergistic Activation Mediator (SAM) transcription activation system to rescue CD200R expression. Lentiviral CD200R with the SAM activation system (LV-CD200R) was transduced into the RVM at 1w after CCI-ION. CD200R gene expression was significantly upregulated in LV-CD200R-treated animals at 3 w after the transduction. While the mechanical hypersensitivity remained in control mice, it was significantly decreased in mice treated with LV-CD200R. CCI-induced upregulation of IL-1beta and downregulated IL-10 proteins were reversed in animals with overexpression of CD200R. Intra-RVM injection of the CD200R agonist CD200-Fc chimera attenuated CCI-induced hyperalgesia. The conditioned place avoidance (CPA) behavior was also significantly reduced after CD-200R activation. Our findings suggest that disrupted inhibitory CD200-CD200R signaling in the RVM contributes to the emergence of chronic pain.

Disclosures: **W. Guo:** None. **J. yang:** None. **C. Bian:** None. **S. Zou:** None. **F. Wei:** None. **K. Ren:** None.

Poster

PSTR081. Amygdala, Hypothalamus, and Medulla

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.23/V16

Topic: D.02. Somatosensation – Pain

Support: CIHR Project Grant

Title: A spinal cord and brainstem fMRI study of the differential effect of mood modulation on pain perception in healthy participants

Authors: *H. ALGITAMI[1], M. UMRAW[2], S. HASSANPOUR[3], P. W. STROMAN[4]; [2]Queen's Univ., [1]Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada; [3]Queen's Univ. Ctr. for Neurosci. Studies, Kingston, ON, Canada; [4]Queen's Univ., Queens Univ., Kingston, ON, Canada

Abstract: The experience of pain involves sensory and affective components, both contributing to pathological pain conditions. Moreover, chronic pain conditions are often comorbid with mood disorders, and both are characterized by persistent negative mood. Although the relationship between negative mood and pain is well established, how they influence each other remains unclear. Therefore, the aim of this study was to use fMRI of the spinal cord and brainstem to identify the neural correlates of how negative mood alters pain perception. Alterations to pain perception occur mainly in the spinal cord and brainstem, via a process called descending pain modulation. This is where brainstem regions receive integrated input from various areas of the brain and spinal cord and are believed to modulate nociception accordingly. Previous work in our lab has developed the necessary fMRI methods to enable the investigation of nociceptive processing in these regions. We hypothesize that there are observable differences in BOLD signal fluctuations between the negative and neutral mood conditions, which reflect the role of negative mood on pain modulation. fMRI data were obtained from a previous mood modulation study conducted in our lab, involving 19 healthy female participants aged 18-30. The study involved fMRI of the spinal cord and brainstem, along with thermal stimulation of the right hand at a calibrated temperature. The International Affective Picture System (IAPS) was used to perform negative and neutral mood modulation in the MRI environment. Participants rated their pain after each combined run of mood modulation and thermal stimulation. A novel network connectivity analysis method was used to assess differences in BOLD signal fluctuations between the negative and neutral study groups. The results indicate that mood modulation occurs in two distinct patterns across people, regardless of study condition (neutral vs. negative). Some connectivity differences between the two patterns are consistent with descending pain modulation. For example, one pattern of differences between negative and neutral study groups showed increased signaling to the spinal cord, coupled with decreased signaling to the NRM and NGc. In contrast, the other pattern showed decreased signaling to the spinal cord, and no clear difference in signaling to the NRM and NGc. The observed differences between the two patterns explain the lack of homogeneity within each study group. Although the presence of mood modulation is discussed here, the factors that lead to its differential effect across people are unknown, and therefore need to be investigated further.

Disclosures: H. Algitami: None. **M. Umraw:** None. **S. Hassanpour:** None. **P.W. Stroman:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.01/V17

Topic: D.06. Vision

Support: NIH Grant U19NS118246

Title: Behavioral and neural correlates of causal inference in motion perception

Authors: *Y. DONG[1], G. F. DIRISIO[2], B. RABAH[1], Z.-X. XU[1], A. ANZAI[1], G. C. DEANGELIS[1];
[1]Univ. of Rochester, Rochester, NY; [2]Univ. of Chicago, Chicago, IL

Abstract: Retinal image motion arises from the combined effects of self-motion and object movement, posing a challenge for the visual system to infer causal relationships. When the retinal image motion of an object differs sufficiently from the optic flow produced by self-motion, the brain subtracts the optic flow vector to estimate object motion relative to the world. This process, called flow parsing (Warren & Rushton, 2009), produces repulsive perceptual biases that have been demonstrated in macaques (Peltier et al. 2020). However, sensory observations are noisy, and there is a slow-speed prior for object motion. Thus, when object motion on the retina is similar to local optic flow produced by self-motion, the observer might infer that the object is stationary in the world and its image motion is caused by self-motion. In this case, motion integration is expected to bias perceived object motion toward the optic flow, leading to an attractive perceptual bias. To test this prediction and identify neural correlates in the visual cortex, we trained a monkey in a motion discrimination task and recorded neural activity from area MT. The task involved discriminating the leftward or rightward motion of a patch of random dots relative to a reference direction. Optic flow simulated three self-motion conditions in which the optic flow vector at the object's location was either leftward, rightward, or neutral with respect to the task reference. As expected for motion integration, the monkey's choices exhibited attractive biases induced by optic flow in the leftward and rightward flow conditions, with larger shifts in psychometric curves compared to the neutral condition. These attractive biases depend systematically on the optic flow angle relative to the object, as well as eccentricity. We recorded population responses in area MT using 32-channel linear arrays. Analyses reveal that some MT neurons exhibit response modulations that depend on optic flow conditions. Furthermore, applying a population decoder to simultaneously recorded neurons (single-session decoding) reveals attractive shifts in predicted psychometric curves in the same direction as, but substantially weaker than, behavioral biases. These findings establish a shift in perceptual biases from repulsive (i.e., flow parsing) to attractive (i.e., motion integration) as the image motion of an object becomes more similar to background optic flow resulting from self-motion. This suggests a causal inference process underlying motion perception in macaques. Moreover, our preliminary neural recordings suggest that activity in area MT may at least partially reflect these causal inference computations.

Disclosures: Y. Dong: None. **G.F. DiRisio:** None. **B. Rabah:** None. **Z. Xu:** None. **A. Anzai:** None. **G.C. DeAngelis:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.02/V18

Topic: D.06. Vision

Support: NSF RI 1704436
NSF DBI 2015317

Title: Design of a synthetic nervous system for visual motion estimation based on the visual motion pathways within Drosophila melanogaster

Authors: *W. NOURSE[1], N. SZCZECINSKI[2], R. QUINN[1];
[1]Case Western Reserve Univ., Cleveland, OH; [2]West Virginia Univ., Morgantown, WV

Abstract: A continuing goal in the robotics community is to develop robots with the dynamic capabilities and resilience of animals, with one particular focus being on adding the influence of visual information to improve the adaptability of robotic systems. One promising approach is to design robotic controllers using neuromorphic networks of neurons with biologically inspired dynamics, also known as synthetic nervous systems (SNS). Much is known about the circuitry within the *Drosophila melanogaster* optic lobe, making it a convenient inspiration for robotic vision systems. For visual motion processing in particular, the *Drosophila* nervous system contains many of the same logical elements as that of mammals and vertebrates, but does so with three orders of magnitude fewer neurons in the visual system. An additional advantage of *Drosophila* over other model organisms is that extensive work has been done in recent years to create a full connectome of their brains, and the visual system in particular has been extensively studied. The motion vision pathway is extremely important for adaptive behavior in *Drosophila*, aiding in estimation of body motion and enabling rapid response to oncoming threats. Previous work has adapted this circuitry to robotics and SNS networks, but these studies were performed before the wide breadth and depth of connectivity information from connectomic analysis for *Drosophila* became available. We present an SNS network which measures optic flow for both rising and falling brightness levels, using inspiration from the current body of knowledge about connectivity and activity within the *Drosophila* optic lobe to create a reduced model suitable for robotic implementation. The SNS network is tuned using local analytic design rules based on responses to simplified stimuli, in order to generate local and global directional selectivity. The performance of this SNS is evaluated on simulated and recorded data from a mobile robotic platform with stereo vision, and the network acts as a stepping point towards visual locomotion control in our hexapod robot inspired by the anatomy of *Drosophila*, *Drosophibot*.

Disclosures: W. Nourse: None. **N. Szczecinski:** None. **R. Quinn:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.03/V19

Topic: D.06. Vision

Support: Department of Psychological and Brain Sciences, Dartmouth College

Title: Transformational apparent motion in a recurrent neural network

Authors: *S. SALEKI[1], P. CAVANAGH[2,3], P. U. TSE[1];
[1]Dartmouth Col., Hanover, NH; [2]York Univ., Toronto, ON, Canada; [3]Glendon Col., Toronto, ON, Canada

Abstract: Sudden onset of a shape that connects two disjoint static figures can induce perception of motion in the form of a continuous shape-change of one or both figures. We previously proposed that the direction of this Transformational Apparent Motion (TAM) is determined through four distinct processing stages: feature encoding, meta-featural shape parsing, shape and contour matching, and motion interpolation (Saleki et al., 2022). Here, using a Recurrent Neural Network (RNN, 256 fully-connected hidden units), we further explored the processing involved in the perception of this illusory motion. We trained an RNN using a reinforcement learning framework on a task with various TAM and continuous shape-change stimuli. Each stimulus configuration was labeled "to the left", "to the right", or "colliding in the middle" according to the illusory motion direction reported in previous studies with human participants. The RNN was able to learn the task completely (100% accuracy on test dataset). To evaluate feature independence, we tested the network on separate datasets comprised of different solid shapes as well as shapes defined only by their outlines. The network achieved significant above-chance performance in these tasks as well, showing similar characteristics in most of the following analyses. Principle Component Analysis revealed that network activity in different stimulus conditions diverged after the onset of the connecting stimulus on each trial (simulated with 4 timesteps for the equivalent of 200 ms) and occupied different parts of the activity space by the end of the trial. This was confirmed by Representational Similarity Analysis of the whole-network activity, indicating high dissimilarity of representations for different stimulus configurations. Furthermore, using hierarchical clustering analysis, we found clusters of units with different characteristic response profiles. Lesion studies identified the role of each cluster in the performance and generalization capabilities of the network, indicating different subprocesses involved in this task in accordance with our previously proposed multi-stage model. Our findings provide mechanistic insights into the processes that underlie the direction of motion perception in TAM.

Disclosures: S. Saleki: None. **P. Cavanagh:** None. **P.U. Tse:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.04/V20

Topic: D.06. Vision

Support: U19NS118246

Title: Viewing geometry inferred from optic flow strongly biases perception of motion and depth: behavior and neural correlates

Authors: *Z. XU, J. PANG, A. ANZAI, G. C. DEANGELIS;
Brain and Cognitive Sciences, Ctr. for Visual Sci., Univ. of Rochester, Rochester, NY

Abstract: Humans and other animals move their bodies to navigate and interact with the world. These movements pose a challenge for sensory systems: sensory consequences of one's actions must be filtered out to form an accurate percept of the world. Here, we examine how inferred viewing geometry alters perceptual compensation for smooth pursuit eye movements. Depending on the viewing geometry, one can use the combination of retinal image motion and eye movements to compute different quantities. For example, during a pure eye rotation, head-centered velocity can be computed by adding retinal and eye velocities (coordinate transformation). In contrast, when the eye translates and counter-rotates to fixate a world-fixed target, depth can be estimated as the ratio between retinal and eye velocities (depth from motion parallax). Does the brain flexibly and automatically perform the appropriate computations depending on the inferred viewing geometry? What are the neural bases of such computations? We conducted human psychophysics to measure perceptual biases and primate electrophysiology to characterize neural responses under different simulated viewing geometries.
We presented distinct optic flow patterns to simulate different viewing geometries while participants viewed an object that moved with a fixed set of directions on the retina. Human participants reported their perceived direction of the object by adjusting a dial or reported perceived depth in a binary (near vs. far) discrimination task. Participants showed different response patterns depending on the viewing geometry inferred from optic flow, exhibiting opposite biases of perceived motion direction or perceived depth in the two simulated viewing geometries. Importantly, these context-dependent perceptual biases occur automatically without any explicit feedback or training.
We presented the same stimuli to macaques while recording neural activity in the middle temporal (MT) area using multi-electrode probes. We observed contextual modulations in neural responses even though optic flow was masked around the receptive fields. Population decoding revealed biases in estimated motion direction similar to those seen in human behavior, suggesting that area MT contributes to flexible computations of motion and depth based on viewing geometry.
Our study reveals that humans and macaques use optic flow to infer the 3D viewing geometry and compute motion and depth accordingly. In contrast to the traditional view that area MT encodes local 2D motion, our neural data demonstrate novel contextual modulations based on inferred viewing geometry that may be involved in coding higher-level perceptual variables.

Disclosures: Z. Xu: None. **J. Pang:** None. **A. Anzai:** None. **G.C. DeAngelis:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.05/V21

Topic: D.06. Vision

Support: NIH Grant EY029438
NIH Grant P51 OD011106
NIH Grant EY035005

Title: Distinct effects of electrical microsimulation in macaque areas MT and FST on 3D motion perception

Authors: *Z. ZHU[1], L. THOMPSON[2], B. KIM[1], A. ROSENBERG[1];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Accurate perception of 3D object motion is vital to survival. In contrast to 2D motion processing, 3D processing depends critically on computations that combine retinal motion signals from both eyes. We previously found that a 2D-to-3D transformation of visual motion signals occurs across the macaque middle temporal (MT) area and the fundus of the superior temporal sulcus (FST). In that work, monkeys discriminated between toward or away motion signaled by: (1) combined stereoscopic and perspective cues, (2) stereoscopic cues, (3) left-eye perspective cues, and (4) right-eye perspective cues. Critically, the trajectories produced opposite net 2D retinal motions in the two eyes, allowing 2D selectivity (indicated by opposite 3D direction preferences for left- and right-eye perspective cues) and 3D selectivity (cue-invariant preferences) to be distinguished. Here we hypothesized that the predominantly 2D output of MT might provide eye-specific retinal motion signals which are integrated to create cue-invariant 3D object motion selectivity in FST. We tested this hypothesis by applying electrical microstimulation (EM) to 2D or 3D selective neurons during the 3D motion discrimination task. As hypothesized, the EM of neurons with cue-invariant 3D motion selectivity, which were predominantly located in FST, resulted in cue-invariant perceptual biases that increased with the strength of the neurons' 3D selectivity. Most critically, the EM of 2D selective neurons also produced cue-invariant perceptual biases, despite that they had incongruent motion preferences across the cue conditions. These perceptual biases were well-predicted by linear models that included 2D direction selectivity, ocular dominance (OD), and cortical area. In particular, the magnitude of the perceptual biases induced by the EM of 2D selective neurons depended on the strength of stimulus selectivity in MT and was drastically smaller in FST. The results imply that MT neurons with 2D direction selectivity and OD contribute to the downstream computation of cue-invariant 3D motion representations. Moreover, the results are consistent with FST representing the full span of 3D motion directions and suggest that, of the neuronal populations studied here, 3D selective FST neurons contribute most directly to the perception of toward/away motion. Collectively, the results reveal distinct causal relationships between neuronal activity in MT and FST and 3D object motion perception, and support the hypothesis that cue-invariant 3D motion selectivity at the level of FST is computed by selectively integrating the output of MT neurons with 2D direction selectivity and OD.

Disclosures: Z. Zhu: None. **L. Thompson:** None. **B. Kim:** None. **A. Rosenberg:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.06/V22

Topic: D.06. Vision

Title: Does assigning intentions to others involve visual motion processing?

Authors: M. GÖRNER, M. SHAFIEI, ***P. THIER**;
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Abstract: We use others' gaze to identify their object of attention. Guterstam and colleagues (Progr. Neurobiol., 2020; PNAS, 2020) suggested that the capability to link the gaze of observed persons to their object of interest is mediated by an imaginary "gaze beam" that emanates from the others' eyes and moves through space. The central tenet of this hypothesis is that the gaze beam recruits the visual motion processing system. They provided evidence for this hypothesis by showing that whenever an observer perceives another person looking towards an object the observer exhibits "motion adaption"-like effects in a subsequent motion-detection task. Görner et al. (PNAS, 2020) argued that the experimental evidence supports not only this "gaze beam hypothesis" but also a different interpretation, namely the beholder´s understanding that the other displays a particular object-related intention. We refer to this interpretation as the "intentional binding hypothesis". This assignment of an intention may involve the prediction of an upcoming movement of the observed person engaging the same system. To critically compare the explanatory power of the two hypotheses, we replicated and extended the original psychophysical study of Guterstam and colleagues. The data was analyzed using Bayesian methods and we collected data until either the criterion of strong evidence (BF >= 10) or a threshold for the upper limit of the amount of data, set in order not to overstrain subjects, was reached. The study is of confirmatory nature and pre-registered at OSF. The data obtained so far (9 participants at the time of writing) suggests that both hypotheses in their original form - predicting motion adaptation effects - are likely to be false. What we found are substantial interindividual differences, not only quantitative, in effect sizes, but especially qualitatively, in effect directions. In our sample we did not find any participant who fully met all of the predictions of the gaze beam nor of the intentional binding hypothesis. For most participants and conditions we have found null effects. Two participants exhibit the predicted "motion adaptation"-like effect but, most interestingly, also some with a reverse effect not predicted by either hypothesis. Both types of effects were present in the original as well as in our new control conditions. An apparent explanation for this heterogeneity is that the individual effects depend on the person's interpretation of the given scene and that this interpretation can be different depending on individual biases.

Disclosures: **M. Görner:** None. **M. Shafiei:** None. **P. Thier:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.07/Web Only

Topic: D.06. Vision

Title: Top-down effects of attention on the action observation network

Authors: *A. EROGLU[1,3], B. A. URGEN[2,3];
[2]Psychology, [1]Bilkent Univ., Ankara, Turkey; [3]Aysel Sabuncu Brain Res. Ctr. and Natl. Magnetic Resonance Res. Ctr. (UMRAM), Bilkent Univ., Ankara, Turkey

Abstract: Visual perception of others' actions plays a crucial role in our lives as we constantly process dynamic visual cues in real-life situations. Perceiving actions recruits the Action Observation Network (AON) that consists of the posterior superior temporal sulcus (pSTS), parietal and premotor cortex. A significant limitation in existing research is the neglect of top-down effects, such as attention, which is prevalent in real-life scenarios. Many studies focus solely on passive viewing, disregarding the potential impact of these top-down influences, with only a few exceptions in recent research. To address this research gap, we designed a functional magnetic resonance imaging (fMRI) experiment consisting of two sessions involving the participation of 27 healthy individuals. For the experiment, we shooted a set of eight action videos featuring different actors, effectors, and targets, all centered around the pushing action. In the first fMRI session (active session), participants were given 3 tasks in which they attended various aspects of the action videos including the actor, effector, and target of the action. In the second session (passive session), participants watched the videos without any task. To analyze the data acquired from the fMRI scans, we extracted three regions of interest (ROIs) from the passive viewing session, namely the pSTS, parietal, and premotor brain regions. Afterwards, we used these ROIs to perform model-based representational similarity analysis (RSA) on the data of the active session. The models included a task model, three feature models including actor, effector, and target models, and a low-level visual model. The results showed that the task model significantly correlated with neural patterns in each region of interest (ROI) whereas the feature models and the low-level visual model did not correlate with neural patterns in any of the ROIs. These findings indicate that top-down attention has a strong influence on every stage of the action observation network (AON) and necessitates the incorporation of top-down signals in computational modelling studies.

Disclosures: A. Eroglu: None. **B.A. Urgen:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.08/V23

Topic: D.06. Vision

Title: A CNN mimicking visual analysis for reflexive manual response exhibits representations like those of neurons in the hierarchical visual motion analysis

Authors: *H. GOMI;
NTT Communication Sci. Labs, Kanagawa, Japan

Abstract: We can successfully control our arms to pick up a cup on the table even when our body is moving. This ability is partially realized by a function that arm movement is regulated in real time based on the visual motion information detected by the retina. To elucidate the information processing realizing this function, we have shown spatiotemporal frequency tuning and stimulus area tuning of the visual motion analysis for the manual following response (MFR) (Gomi et al. 2006; 2013). Additionally, we recently found that the convolutional neural network (CNN) model trained to estimate self-motion from visual image sequence recorded during human actions exhibits similar stimulus tuning properties to the MFR. This suggests that information processing to decode self-motion from visual information may be involved in MFR generation process (Nakamura and Gomi 2023). On the other hand, the brain MT/MST areas are thought to be involved in generating MFR (Amano et al. 2009). Therefore, in this study, we investigated whether kernel outputs of the learned CNN exhibit stimulus tuning properties similar to those of the brain hierarchical visual motion analysis. The CNN consists of six convolutional-kernel layers with linear full connections, which was trained to decode 6DoF head-camera motion. In the 1st layer, the spatial-frequency peaks of kernels were widely distributed from 0.1 c/deg to 1.0 c/deg, but many kernels in the 2nd to 6th layers had peaks at lower spatial frequencies of 0.5 c/deg. On the other hand, the temporal-frequency peaks of many kernels were over 10 Hz although some kernels had lower temporal frequency peak. This trend is similar to the characteristics of LGN cells, but different from those of V1 cells. In the higher layer, temporal-frequency peaks were densely distributed over 10 Hz. The distribution of directionality index of the CNN first-layer kernels looks similar to that of the V1 cells (Wang and Movshon 2016). In addition, we observed negative correlation between the spatial and temporal frequency peaks of kernels in each layer, as observed in MT cells (Prieb et al. 2003). As for the pattern and component direction selectivity, the 1st- and 2nd-layer kernels showed high partial correlation coefficients for component prediction while many kernels in the 6th layer had high partial correlation coefficients for pattern prediction. This is similar to the distribution difference in partial correlations between V1 and MT/MST cells (Movshon et al. 1985; Khawaja et al. 2013). These results are consistent to an idea that MFR is driven by an estimated self-motion from visual information for quickly correcting the reaching movement for interacting with external objects.

Disclosures: H. Gomi: None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.09/V24

Topic: D.06. Vision

Support: NIH Grant EY027853-01
Kavli NDI predoctoral fellowship

Title: Development of motion vision in ferrets: a network perspective

Authors: *B. R. NANFITO, K. J. NIELSEN;
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Abstract: Decades of investigation have characterized the hierarchical nature of visual cortical processing in adult animals, but how activity in one visual area influences the functional development of response properties in another is not well understood. Cortical visual development is thought to begin with the primary visual cortex (V1) and subsequently propagate up the hierarchy to higher order visual areas. However, studies in primates have demonstrated the early maturation of higher order motion area MT, suggesting network-level interactions across the hierarchy are possible during development of the motion pathway. In the present study, we use the visual motion pathway of ferrets, specifically V1 and posterior suprasylvian sulcus (PSS), as a platform to investigate the causal influence that different visual areas exert on each other's functional development. We have previously found that at least in terms of selectivity for motion direction, PSS matures as early as V1. Additionally, new preliminary anatomical data show that in juvenile but not in adult animals, PSS receives a strong direct projection from the lateral geniculate nucleus in the thalamus. These observations raise questions about the spatiotemporal sequence and interdependencies of the functional development of at least V1 and PSS. Here, using extracellular electrophysiology to simultaneously record neural activity from V1 and PSS, in conjunction with reversible inactivation of either area by cooling the cortical surface, we are characterizing their dependencies at different ages. Preliminary data show that in juveniles, but not adults, PSS neurons retain some of their responsiveness and tuning properties when V1 is inactivated. To directly test how either area depends on the other for functional maturation of its response properties, we make use of a visual stimulus protocol ("training") that induces rapid maturation of direction selectivity in both V1 and PSS in juvenile, visually naïve animals. Training consists of repeated stimulation with gratings drifting in one of two directions for 8 hours. In the context of this training paradigm, preliminary data suggest that after training with V1 cooled selectively during stimulus presentations, PSS neurons increase their direction selectivity without a concomitant increase in direction selectivity of V1 neurons. This dissociation demonstrates that PSS direction selectivity can develop - at least to some degree - independently of V1 input. In general, these experiments confirm the need to study development at the network level.

Disclosures: B.R. Nanfito: None. **K.J. Nielsen:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.10/V25

Topic: D.06. Vision

Title: Retina structure shapes neuron function in Drosophila motion vision

Authors: *A. ZHAO[1], E. GRUNTMAN[3], A. NERN, 20147[2], N. IYER[2], E. ROGERS[2], S. KOSKELA[3], I. SIWANOWICZ[2], M. DREHER[4], M. FLYNN[2], C. LAUGHLAND[2], H. LUDWIG[2], A. THOMSON[2], C. MORAN[5], B. GEZAHEGN[2], D. BOCK[6], M. B. REISER[4]; [1]Janelia, ASHBURN, VA; [2]Janelia, Ashburn, VA; [3]Janelia Res. Campus, Ashburn, VA; [4]HHMI / Janelia, Ashburn, VA; [5]janelia, ashburn, VA; [6]Neurolog. Sci., Univ. of Vermont, Burlington, VT

Abstract: The changes in the visual scene during movement generate *optic flow* patterns, which are used by many animals to guide navigation. Optic flow is first estimated in small patches by directionally selective neurons, such as T4 neurons in flies. This direction selectivity results from asymmetric inputs of retinotopically arranged columnar cells. There are 4 subtypes of T4 neurons at each retina location and their preferred directions (PDs) of motion correlate with their dendrites' orientation. Near the center of the eye, the PDs align well with the 4 cardinal directions of body translation (forward, backward, up, and down), but across the eye, a configuration of orthogonal PDs aligned to cardinal axes is not possible. Take a simple translational motion as an example, whereas all the objects in the environment moves in a parallel fashion, the induced optic flow vectors projected on the curved compound eyes are no longer parallel to each other. We measured the local PDs of one T4 subtype using electrophysiology and found evidence for non-parallel directions at different retinal locations. Two simple mechanisms could explain this location-dependent variation: (i) T4 dendrite rotates consistently with respect to their retinotopic inputs; (ii) T4 arborization remains constant while input neurons sample space in a non-uniform fashion. To distinguish these possibilities and to understand the global organization of directional tuning across the array of directionally selective neurons, we mapped the T4 PDs throughout the field of view. We first reconstructed all the Mi1 neurons, a primary T4 input, in a full brain EM volume to establish a columnar, anatomical reference frame. We then reconstructed hundreds of T4 neurons across the eye and computed their PDs based on the dendritic orientations. We compared the PD vectors in the common reference frame and found a stereotypical pattern that's largely consistent with mechanism (ii). To test the proposal of non-uniform mapping of visual space, we scanned a whole fly head using μCT to determine the viewing direction of every ommatidium, and established a 1-to-1 mapping between viewing directions and columnar inputs. This mapping in turn allowed us to map T4 PDs to the eye coordinates. We identified a systematic change in the arrangement of neighboring ommatidia viewing directions that largely explained the observed location-dependent PD. Furthermore, we discovered that the translation axis best fit to the mostly horizontal-motion-sensitive T4 population is not straight ahead, but about 40° laterally, close to the eye's highest visual acuity zone.

Disclosures: **A. Zhao:** None. **E. Gruntman:** None. **A. Nern:** None. **N. Iyer:** None. **E. Rogers:** None. **S. Koskela:** None. **I. Siwanowicz:** None. **M. Dreher:** None. **M. Flynn:** None. **C. Laughland:** None. **H. Ludwig:** None. **A. Thomson:** None. **C. Moran:** None. **B. Gezahegn:** None. **D. Bock:** None. **M.B. Reiser:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.11/W1

Topic: D.06. Vision

Support: NSERC

Title: Frame induced position shifts extend outside the frame in space but not in time

Authors: *B. M. 'T HART, P. CAVANAGH;
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Abstract: When two probes are flashed at the same physical location within a moving frame, their perceived location can be offset by as much as the frame moves (Özkan et al, PNAS, 2021). Here we examine the extent of the frame's influence in space and time. First, we positioned the flashed probes in front of or behind the frame in depth (or both) using red/cyan anaglyph glasses. The illusion strength was not affected by these depth mismatches. In contrast, placing the flashed probes outside the frame did influence the illusion. The illusion strength dropped to 50% magnitude once the probes were 5.4 dva to the left of the frame. In the vertical direction, the 50% decrease required an offset of 6.9 dva between the frame and the probes. Offsets in time from the presentation of the frame caused a complete loss of the illusion. The frame was presented for one to three cycles of left-right motion and when the probes were flashed before or after the frame presentation, there was no illusion, no matter how long the frame had been present. This suggests that the illusion depends on immediately present sensory information without any influence of the frame's motion before or after its actual presence on the screen. In conclusion, the frame effects do extend outside the boundaries of the frame in space but not in time.

Disclosures: B.M. 't Hart: None. **P. Cavanagh:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.12/W2

Topic: D.06. Vision

Support: Howard Hughes Medical Institute

Title: Investigating the visual motion processing neurons in Drosophila

Authors: *S. KOSKELA, A. NERN, A. ZHAO, E. ROGERS, C. LAUGHLAND, S. MILLER, R. ARRUDA, J. PARK, M. B. REISER;
Janelia Res. Campus, Ashburn, VA

Abstract: Navigating flies rely on visual motion patterns to regulate their flight behaviors. Wide-field motion sensitive cells called lobula plate tangential (LPT) neurons have response properties that match well to visual patterns induced by self-motion and are presumed to contribute to stabilizing course control via reactions commonly known as optomotor behaviors. In larger flies a subset of LPTs has been studied for decades, but only recently has it been possible to describe their anatomy and explore their function in *Drosophila*. Thus far, no LPT has been conclusively assigned a causal role in any specific optomotor reaction. Here, we describe the LPT types innervating lobula plate (LP) layers 1 and 2 and their potential roles in behavioral optomotor responses.

We identified 58 LPT types in *Drosophila melanogaster* based on extensive EM reconstructions. We quantified their morphology and layers of innervation to computationally predict their receptive fields. Based on these predictions, we designed wide-field visual stimuli and measured the behavioral responses of tethered, flying flies with an updated high speed, high spatial resolution LED display. We discovered that the optomotor response of wildtype flies (females) to a drifting vertical grating was strongest for patterns presented in front of the fly while stimuli presented at the sides evoked no response. To identify the LPT types underlying this behavior, we examined LPTs in layers 1 and 2 with innervation corresponding to frontal field of view. We generated candidate split-GAL4 driver lines for the cell types, that morphologically match EM reconstructions. We silenced specific LPTs by expressing Kir2.1 and compared the behavioral responses to wide-field motion patterns (yaw, sideslip, roll, lift) and to those of genetic control flies.

Surprisingly, we have not yet identified any LPT type, that when silenced, dramatically reduces specific optomotor turning reactions. In most cases the reactions of flies with individually silenced LPT types do not differ from the control fly behavior. Silencing well-known LPTs, the HS and H2, appears to result in enhanced turning, despite these cells being excitatory. Possibly, (1) silencing individual LPTs does not impede turning reactions since the neurons work in concert with redundancy, or (2) the optomotor reactions we are measuring rely on a different set of neurons, or both. We continue to analyze newer EM data to further explore the circuit components of optomotor behaviors and try alternative methods for silencing the cells (transient inactivation). Finally, we are characterizing the visual motion responses of individual LPTs using patch clamp electrophysiology.

Disclosures: S. Koskela: None. **A. Nern:** None. **A. Zhao:** None. **E. Rogers:** None. **C. Laughland:** None. **S. Miller:** None. **R. Arruda:** None. **J. Park:** None. **M.B. Reiser:** None.

Poster

PSTR082. Visual Motion Processing

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.13/W3

Topic: D.06. Vision

Support: NIH grant RO1 EY022443

Title: Neural representation of multiple speeds of spatially separated stimuli in cortical area MT

Authors: A. CHAKRALA, **Y. CAO**, *X. HUANG;
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Abstract: Scene segmentation is fundamental to vision. Motion speed provides an important cue for segmenting objects from visual scenes. The middle temporal (MT) cortex of primates plays a critical role in processing speed information. We have previously characterized how MT neurons represent overlapping stimuli that move at different speeds. In natural vision, it is common for multiple entities to reside at different spatial locations. MT neurons have receptive fields (RFs) that are often large enough to encompass multiple spatially separated stimuli. It is still unclear how MT neurons represent multiple speeds of spatially separated stimuli within the RFs. We recorded the responses of single MT neurons from two fixating macaques. The stimuli were two random-dot square patches placed side by side (left and right), with the border centered on the RFs. The two patches moved at different speeds. The speed of one patch was always four times of the other. We varied the speed pairs from 1.25 and 5°/s to 20 and 80°/s to characterize tuning curves to bi-speed stimuli. To account for potential spatial effects, we used two spatial arrangements of “left-patch fast/right-patch slow” and “left-patch slow/right-patch fast”. We found that the neuronal responses to two speeds showed a bias to the faster speed when both speeds were low (< 20º/s) and a bias to the slower speed when both speeds were high (>30º/s). At low stimulus speeds, the faster stimulus alone elicited a stronger response than the slower stimulus alone at the level of MT population; Whereas at high stimulus speeds, the slower stimulus elicited a stronger response. In essence, our results showed a robust bias toward the stronger stimulus (i.e., Max-like operation) in response to spatially separated stimuli moving at different speeds. Surprisingly, when two speeds, presented alone, elicited roughly equal responses, the response elicited by both speeds was stronger than that of the individual speeds, described as a sublinear summation. In addition to the speed preference, some neurons showed a spatial preference for stimuli at either the left or right side of the RFs. Neurons’ spatial and speed preferences to single stimuli were preserved in their responses to bi-speed stimuli. For example, neurons that preferred the left location and faster speeds of single stimuli showed stronger responses to the “left-fast/right-slow” stimuli than “left-slow/right-fast” stimuli. Thus, subgroups of neurons with different speed and spatial preferences could enable joint encoding of spatial and speed information of two stimuli, providing a heterogeneous neural code for representing multiple visual stimuli and for achieving scene segmentation.

Disclosures: A. Chakrala: None. **Y. Cao:** None. **X. Huang:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

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Program #/Poster #: PSTR082.14/W4

Topic: D.06. Vision

Support: The Francis Crick Institute PhD studentship

Title: Visuomotor integration gives rise to three-dimensional receptive fields in the primary visual cortex

Authors: *Y. HE, A. BLOT, A. COLAS NIETO, P. ZNAMENSKIY;
The Francis Crick Inst., LONDON, United Kingdom

Abstract: Distinguishing near and far visual cues is an essential computation that animals must carry out to guide behavior using vision. When animals move, self-motion creates optic flow with its speed dependent on the depth of visual cues. This phenomenon, known as motion parallax, enables animals to estimate depth by comparing visual motion and self-motion speeds without relying on binocular vision. As neurons in the mouse primary visual cortex (V1) are broadly modulated by locomotion, we hypothesized that they may integrate vision- and locomotion-related signals to estimate depth from motion parallax. To test this hypothesis, we designed a virtual reality environment for mice, where visual cues were presented at different virtual distances from the mouse and motion parallax was the only cue for depth. We then recorded neuronal activity in V1 using two-photon calcium imaging. We found that a large fraction of the excitatory neurons in layer 2/3 of V1 were selective for virtual depth. Neurons with different depth preferences were spatially intermingled, with nearby cells often tuned to disparate depths. Many neurons responded selectively to visual stimuli presented at a specific retinotopic location and virtual depth, demonstrating that during active locomotion V1 neuronal responses can be characterized by three-dimensional receptive fields. Moreover, depth tuning could not be fully accounted for by either running speed or optic flow speed tuning in isolation but arose from the integration of both signals. Specifically, depth selectivity of V1 neurons was explained by the ratio of preferred running and optic flow speeds. In addition, the closed-loop coupling of locomotion and optic flow feedback was required for accurate decoding of depth from V1 population activity. These results suggest that the conjunctive coding of visual motion speed and self-motion speed in mouse V1 may serve as the neural mechanism underlying depth estimation from motion parallax during active locomotion.

Disclosures: Y. He: None. **A. Blot:** None. **A. Colas Nieto:** None. **P. Znamenskiy:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

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Program #/Poster #: PSTR082.15/Web Only

Topic: D.06. Vision

Support: DFG HO2002/10-3 No. 149341228

Title: Altered perception of the bistable motion quartet in albinism

Authors: *K. O. AL-NOSAIRY[1], E. QUANZ[1], C. M. EICK[2], J. KORNMEIER[3,4,5], M. HOFFMANN[1,6];
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Abstract: The motion quartet (MQ) comprises a pair of dots located on an alternating pair of diagonal corners of an imaginary rectangle. It is perceived as two dots moving either horizontally or vertically in opposite directions depending on the ratio between horizontal and vertical dot distances (aspect ratio, "AR"). At AR = 1, i.e. a square, the alternating perception of horizontal and vertical motion should be balanced. In contrast, a 'vertical bias', i.e. a prevalence of the perception of vertical motion, has previously been demonstrated. This perceptual asymmetry for the square version of the MQ is assumed to be due to the perception of horizontal motion requiring integration across hemispheres whereas the perception of vertical motion requires only intrahemispheric processing. In albinism there is an increased crossing of the optic nerve fibers at the optic chiasm such that each hemisphere receives input from the contralateral eye that comprises both visual hemifields. This might result in a decreased/eliminated vertical bias. In the present study, the effect of albinotic optic nerve misrouting on MQ-perception (AL, n=14) was compared to healthy controls (HC, n=11). In order to exclude albinotic nystagmus as a potential confound, patients with nystagmus in the absence of optic nerve misrouting we also included (NY, n=12). Motion perception was tested by presenting MQ-two dot pairs sequentially for 150 ms. Horizontal and vertical distances between the dots were varied to present MQ with different ARs, spanning from 0.75 to 1.25 (in 0.1 steps) to induce a systematic variation from horizontal to vertical motion perception. For HC, the frequency of vertical motion perception increased as a sigmoid function with increasing AR exhibiting the expected vertical bias, i.e. vertical percepts for 55% of trials. AL showed a surprisingly clear horizontal bias with horizontal motion percepts in 87% of the trials. The NY group was in between with horizontal perception in 62% of the trials. Nystagmus itself does explain this pattern of results because AL and NY groups had comparable fixation stabilities within 2° and 4°. The strong horizontal bias observed in AL and NY might partly result from the horizontal nystagmus in both groups. The even stronger horizontal bias in AL indicates that the intra-hemispherical co-representation of both visual hemifields may play an additional role. The altered perception of the bistable MQ in AL might offer an opportunity to (i) understand the interplay of stability and plasticity in altered visual pathway conditions and (ii) identify visual pathway abnormalities with a perception-based test with potential applications in diagnostics.

Disclosures: K.O. Al-Nosairy: None. **E. Quanz:** None. **C.M. Eick:** None. **J. Kornmeier:** None. **M. Hoffmann:** None.

Poster

PSTR082. Visual Motion Processing

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Program #/Poster #: PSTR082.16/W5

Topic: D.06. Vision

Support: NSF IIS-2113197
NIH R00EY032179

Title: Hierarchical VAEs provide a normative account of motion processing in the primate brain

Authors: *H. VAFAII[1], J. L. YATES[2], D. A. BUTTS[3];
[1]Univ. of Maryland (UMD), College Park, MD; [2]Univ. of California, Berkeley, Berkeley, CA;
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Abstract: The relationship between perception and inference, as postulated by Helmholtz in the 19th century, is paralleled in modern machine learning by generative models like Variational Autoencoders (VAEs) and their hierarchical variants. Here, we evaluate the role of hierarchical inference and its alignment with brain function in the domain of motion perception. We introduce a novel synthetic data framework, Retinal Optic Flow Learning (ROFL), that enables control over motion statistics and their causes. We then test the performance of unsupervised models on two critical downstream tasks: predicting ground truth variables (e.g., object motion) and predicting the responses of single neurons from area MT of the primate dorsal pathway. Importantly, this framework allows us to manipulate both the architectures of the models and the causal structure of the world they are trained on. We found that a single inductive bias, hierarchical latent structure, yields several improvements. First, it improves the linear decodability of ground truth variables and does so in a sparse and disentangled manner. Second, hierarchical VAEs outperform previous state-of-the-art models in predicting MT neuron responses with a performance gain of over 2x and result in sparse latent-to-neuron relationships. Third, these results depend on the causal structure of the world, indicating that alignment between brains and artificial neural networks depends not only on architecture but on matching the stimulus statistics of the organism. Collectively, these results suggest that the brain engages in hierarchical Bayesian inference to comprehend the state of the world and that this functional organization can be effectively captured by hierarchical VAEs.

Disclosures: H. Vafaii: None. **J.L. Yates:** None. **D.A. Butts:** None.

Poster

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Program #/Poster #: PSTR082.17/W6

Topic: D.06. Vision

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 154113120 – SFB 889, project C04

Title: Adaptive and closed-loop sampling methods for a rapid estimation of receptive fields in macaque visual cortex area MST

Authors: *A. EDATHODATHIL, S. TREUE;
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Abstract: How the physical world is represented in the activity of cortical neurons is a key question in neuroscience. Typically, for the visual system, this relationship is studied by presenting well-defined visual stimuli multiple times and then averaging the neuronal response to obtain a neuron's stimulus preferences (tuning curves, spatial receptive fields). For 2-dimensional visual receptive field (RF) estimation, visual stimuli (such as random dot patterns (RDPs)) are repeatedly presented for a few seconds at different positions, followed by an offline analysis of neuronal responses and a RF map is computed (traditional method). We study the macaque visual cortical area MSTd, which contains neurons selective for linear and for complex motion patterns (expansion, rotation, and spirals) which are crucial for optic flow perception. In this study, we use a 'closed-loop electrophysiology' approach aimed at a faster estimation of the preferences of a neuron using 'adaptive sampling' methods. In this approach, the stimulus for an experimental trial is based on the neural data collected from previous trials. We evaluate two adaptive sampling methods: the Nelder-Mead Simplex Algorithm (Nelder & Mead, 1965) and the Bayesian Active Learning (BAL) approach (Pillow & Park, 2016)) for estimating the 2-D preference profile (the RF) of an MST neuron. The simplex algorithm method was able to estimate the center of the RFs with an error as low as 15 to 30% of the RF width, in less than 40 seconds of stimulus presentation (100 ms single RDP presentations time, multiple trials), compared to about 120 seconds in the traditional method (N = 4). The BAL method was also able to estimate the center and the map of the receptive field in about 40 seconds, providing a more detailed description of the RF compared to the simplex algorithm. The RF center estimate error using the BAL method was as low as 10 to 25% of the RF width and the estimate showed less fluctuations compared to the simplex approach. In summary, our data show that adaptive methods are substantially faster in estimating stimulus preferences compared to traditional mapping approaches.

Disclosures: A. Edathodathil: None. **S. Treue:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.18/W7

Topic: D.06. Vision

Title: The Relationship Between Visual Sensitivity to Balance and Visual Motion Detection Thresholds

Authors: *S. DIBIANCA[1], J. GRAY[1], R. J. PETERKA[2], J. J. JEKA[1], H. REIMANN[1]; [1]Univ. of Delaware, Newark, DE; [2]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Background: Visual sensitivity to optic flow for balance control has been shown to be higher in older vs. younger adults, although the underlying mechanism is not well understood. A visual motion detection threshold (VMDT) is an estimate of the smallest detectable movement of the visual field. VMDTs are associated with over 3 times higher odds of failing on a single leg balance stance task compared to visual acuity, contrast sensitivity, and visual field size when adjusted for age, sex, and race. Here, we investigate whether an individual's ability to detect motion influences their sensitivity to visual fall stimuli while walking. In addition, we aim to determine any differences in VMDTs when walking versus standing and standing with optic flow. **Methods:** A cohort of 17 healthy young and 19 healthy old participants walked on a self-paced, instrumented treadmill inside a virtual reality dome. The display showed a pseudo-random rotation of the environment around the anterior/posterior axis at floor level. We calculated visual sensitivity as gain of the frequency response function, i.e., the ratio of medial-lateral center of mass movement and the visual stimulus at the driving frequencies of the visual stimulus, in frequency domain. To measure VMDTs, the same participants performed a 2-alternative forced choice task in which they discriminated between a counterclockwise ("left") and clockwise ("right") rotation of a visual scene projected on the large dome. A 3 down 1 up adaptive staircase algorithm was used to update the amplitude of the rotation. A psychometric curve fit to the participants' responses provided an estimate for the detection threshold. Participants' performed the visual motion detection tests while standing with their head fixated with and without optic flow, as well as while walking. **Results:** Preliminary results indicate a weak positive correlation between the VMDT values and the visual sensitivity measures in walking for both young and older adults. This trend was more pronounced in younger adults. Contrary to our expectations, the direction of this correlation is positive, indicating that the less reliable the visual system is at detecting optic flow movement, the higher their sensitivity is to visual fall stimuli. **Conclusion**: Preliminary results indicate that the ability to detect motion influences the sensitivity to visual stimuli for balance control while walking to a larger degree for young adults compared to older adults. Furthermore, the presence of forward optic flow hindered the ability to detect motion for young adults while aiding the ability for older adults.

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Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

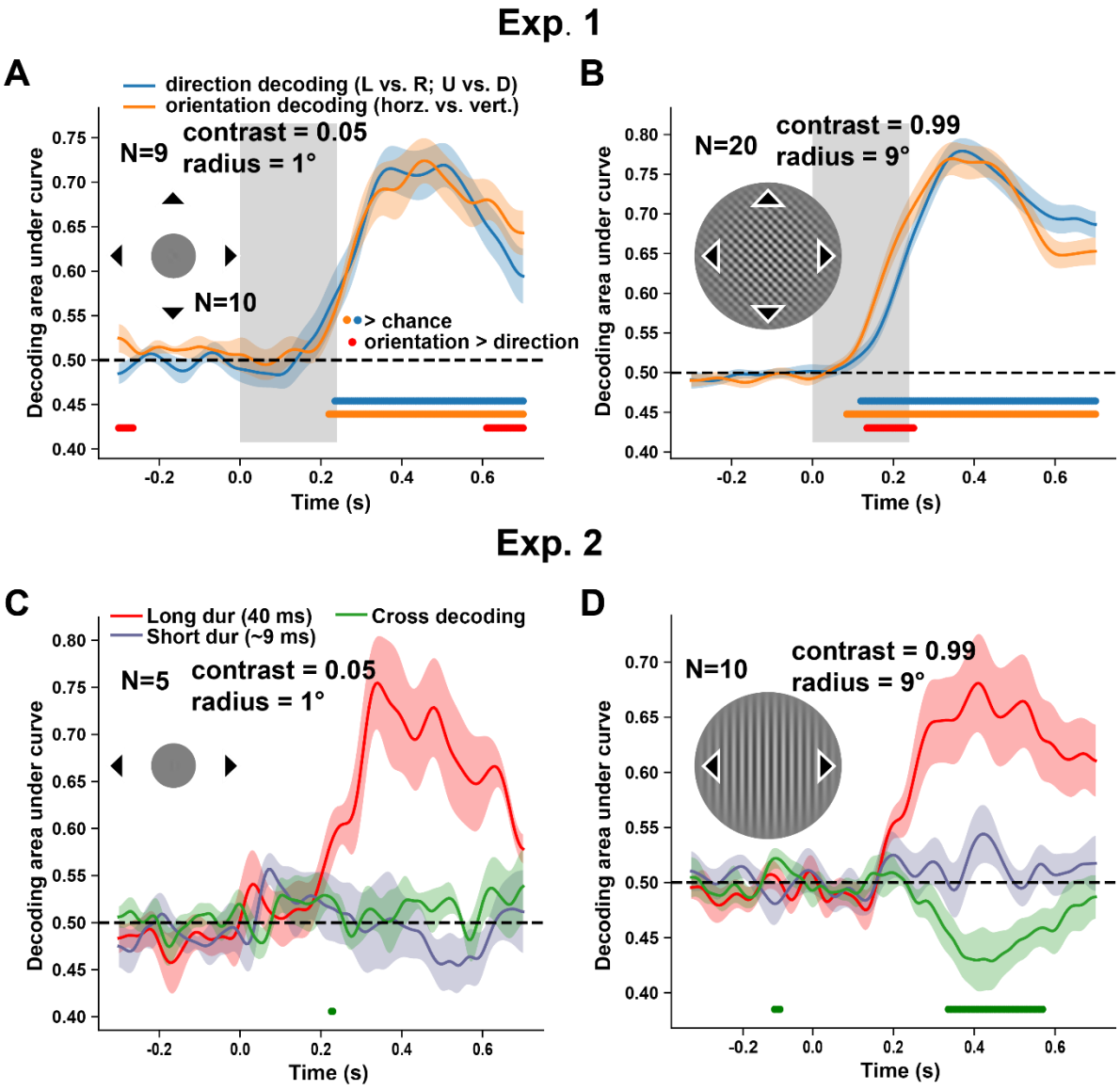
Program #/Poster #: PSTR082.19/W8

Topic: D.06. Vision

Title: Neural correlates of non-directional orientation information in human motion perception

Authors: Y.-X. LU[1,2], F. LI[1,2], P.-R. YANG[1,2], O.-S. KWON[3], D. TADIN[4,5], *R.-Y. ZHANG[1,2]; [2]Shanghai Mental Hlth. Ctr., [1]Shanghai Jiao Tong Univ., Shanghai, China; [3]Ulsan Natl. Institue of Sci. and Technol., Ulsan, Korea, Republic of; [4]Univ. of Rochester, Rochester, NY; [5]Departments of Ophthalmology and Neurosci., Univ. of Rochester Med. Ctr. Rochester, Rochester, NY

Abstract: Motion perception is a fundamental visual function, yet the neural representation of motion direction remains unclear. Here, we provide two pieces of evidence for the critical role of non-directional orientation information in the representation of motion direction in the human brain. First, our previous psychophysical experiments revealed that, when perceiving the motion of large, high contrast (LHC) stimuli, observers first perceive the orientation at which the physically presented direction lies and then perceive its true direction. To investigate its neural substrates, we recorded the EEG signals from 29 human subjects while they performed a 4-AFC (left/right/up/down) direction judgment task on moving plaid stimuli. Time-resolved decoding analyses were performed with respect to the orientation information (2-way decoding; vertical, up/down vs. horizontal, left/right) and the direction information (4-way decoding; left/right/up/down). Consistent with the faster perception of orientation than direction in behavior, decoded orientation information indeed emerged ~50 ms earlier than the direction information. Also, this phenomenon occurred only for LHC (Fig. 1B) but not for small, low contrast stimuli (Fig. 1A). Second, we also showed that observers routinely misperceive the direction of brief stimuli (<10ms) in the direction opposite to what is physically shown. We again recorded the EEG signals from 15 human subjects while they performed a 2-AFC (left/right) direction judgment task on drifting grating stimuli. We applied the 2-way direction classifier trained on the brain signals elicited by unambiguous, long duration stimuli to those of ambiguous, brief stimuli. We found a significant below-chance decoding accuracy, a neural signature indicating the perceived direction opposite to the true direction. Also consistent with the misperception in behavior, this neural signature occurred only for the LHC (Fig. 1D, C) stimuli. In summary, we present novel evidence that non-directional orientation plays a crucial role in representation of visual motion direction.



Disclosures: **Y. Lu:** None. **F. Li:** None. **P. Yang:** None. **O. Kwon:** None. **D. Tadin:** None. **R. Zhang:** None.

Poster

PSTR082. Visual Motion Processing

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Topic: D.06. Vision

Support: ARC CIBF grant CE140100007

Title: Dual encoding of motion cues in cat primary visual cortex

Authors: *Z. TAO[1], Y. J. JUNG[3], &. SIBBERAS[2], A. N. BURKITT[1], M. R. IBBOTSON[2], H. MEFFIN[1];
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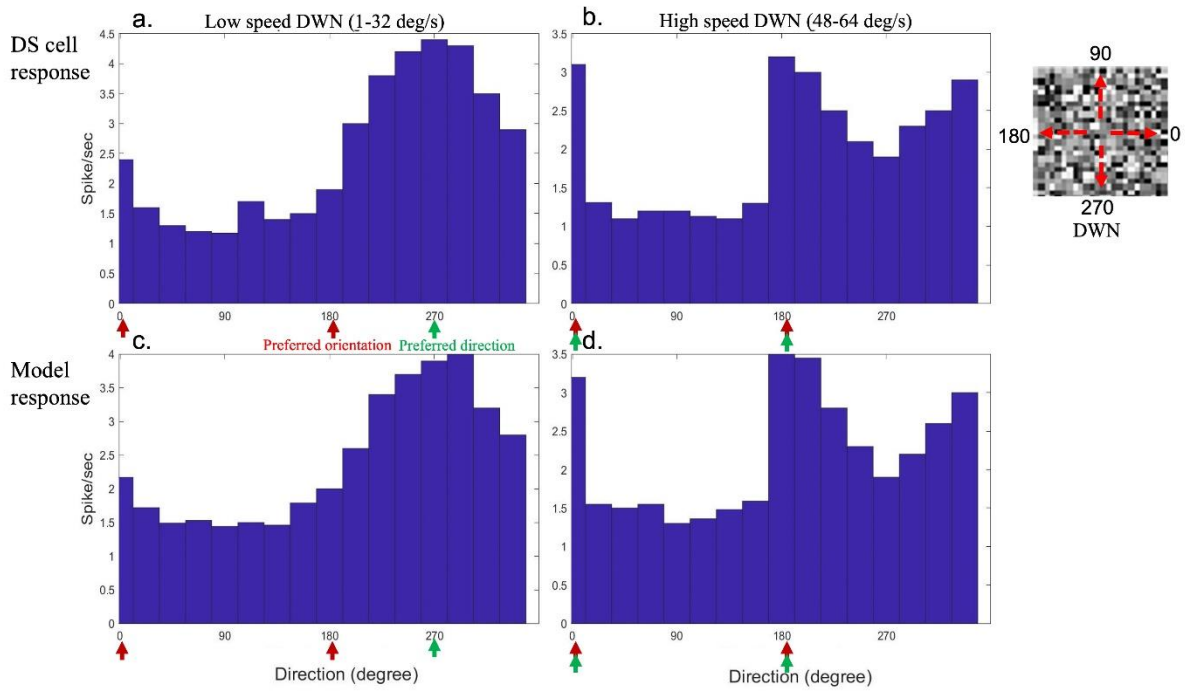
Abstract: The population code in the visual system utilizes multiple motion cues to encode the velocity of objects. In primary visual cortex (V1), one such cue is the tracking of object edges: many neurons tuned to orientation are also tuned to velocity in the direction perpendicular to their preferred orientation. Perceptually, another cue, called motion streak, relates to tracking fast objects, such as dots, that create a smeared perception of motion along their trajectory. In mouse visual cortex, neural correlates of motion streak have been observed in response to high-speed dot motion, with tuning to directions either parallel or perpendicular to the cell's orientation. We studied whether dual tuning, to both motion cues, can be explained by integration via a neuron's spatio-temporal receptive field (STRF). We recorded neural responses in cat V1 to drifting white noise (DWN) of fixed patterns, which contain both edge-like and dot-like features, using 64 speeds (0:1:64 °/s) and 16 directions (0:22.5:337.5°). Responses to drifting gratings were used to classify orientation (OS) and direction-selective (DS) cells. We found 81 neurons tuned to both cues using DWN — edge motion cues and motion streak. Consistent with responses to gratings, at low DWN speeds, DS cells (n = 32) were selective to the direction perpendicular to their preferred orientation (edge motion cues, Fig. a), while OS cells (n = 49) were not direction selective. Conversely, at high speeds, both types preferred the direction parallel to their orientation (motion streak, Fig. b). To investigate the dual tuning mechanism, we inferred a biologically plausible STRF model from electrophysiological data to predict responses to DWN for each cell. We found that the tuning of model responses matches the measured tuning for both low and high speeds in terms of firing rate and direction-selectivity (e.g., DS cell in Fig. c & d, correlation = 0.96; population range: 0.81-0.96). The findings indicate that dual encoding in V1 of the motion cues for object edges and motion streak are explained by the same mechanism, namely integration within the STRF.



Disclosures: **Z. Tao:** None. **Y.J. Jung:** None. **&. Sibberas:** None. **A.N. Burkitt:** None. **M.R. Ibbotson:** None. **H. Meffin:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.21/W10

Topic: H.01. Attention

Title: The effect of peripheral stimulus perception on visual processing in area MT of macaque visual cortex

Authors: *M. CRAYEN[1,2,3], M. ESGHAEI[1], S. TREUE[1,2,4,5];
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Abstract: How the different features of a visual stimulus are integrated into a joint perceptual experience is known as the ‘binding problem’. While its existence is still debated, the use of perceptually ambiguous visual stimuli, i.e., ‘illusions’, can provide valuable insights into the fundamental mechanisms underlying visual information processing and perception.
We trained two rhesus macaques to discern the movement direction of a multi-featured random

dot pattern (RDP). The stimulus consists of a central and a peripheral part, both made up of random dots, colored uniformly either red or green. The peripheral dots move in one of two directions, irrespective of the central dot movements. The coherence of the peripheral dots is variable and defined by the ratio of those dots moving into one direction and those moving in the opposite direction. Central dots are split equally into green and red, with one color moving coherently in one direction, while the other moving in the opposite direction. Alternatively, one half of the dots of one color moved in one direction, while the other half moved in the second direction. This design generates three different perceptual conditions, where peripheral dots, which the monkeys reported, are either a) correctly bound, b) misbound or c) unbound to same-colored central dots. Additionally, the peripheral movement coherence allowed to change the difficulty of the task.
Here we show single cell recordings of the middle temporal visual cortex area MT, which preferably respond to visual motion. Neurons with receptive fields overlapping the central stimulus show a firing rate gain, whenever the monkey's report of the peripheral movement matches the preferred direction of the recorded neuron. This effect reverses when an anti-preferred movement is reported by the monkey. Both effects are observed independently from the actual peripheral movement direction and despite an identical central stimulus in all trials that are compared.
These data suggest that the activity of neurons in the visual cortex area MT, is influenced by erroneous percepts of stimuli that are bound by matching direction and color properties but are located outside of their receptive field. The effect of attention and illusory percepts on the processing of visual stimuli will be subject of further investigation in this project.

Disclosures: **M. Crayen:** None. **M. Esghaei:** None. **S. Treue:** None.

Poster

PSTR082. Visual Motion Processing

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.22/W11

Topic: D.07. Visual Sensory-Motor Processing

Support: NSERC grant RGPIN-2023-03559
CIHR grant MOP-119498

Title: Refractive error measurement using continuous psychophysics and eye tracking

Authors: E. S. PIRSO[1], J. F. MITCHELL[3], *C. BAKER[2];
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Abstract: Finding the best optical correction for refractive errors can be challenging in animal subjects or in human patients who have difficulty with conventional measurement methods. Refractive corrections are of growing concern in vision research due to the high prevalence of

myopia in some colony-reared animals. Existing approaches may involve psychophysical paradigms such as two-alternative forced-choice, requiring extensive training, or retinoscopy, which in animals would require anesthesia. However, tracking of a moving target on a blank background is a natural task that is relatively easy for subjects to learn and execute. Here we explored the use of continuous psychophysics and eye tracking (Bonnen et al, 2015; Knoll et al, 2018) to measure contrast thresholds and assess refractive errors. We employed custom MATLAB-based software with PsychToolbox-3 for stimulus presentation and interfacing with an EyeLink 1000 eye tracker. This approach evaluates refractive errors by monitoring a subject's contrast sensitivity as they track a dynamic visual stimulus with gradually decreasing contrast. Applying this approach to the tracking task of a Gabor stimulus, we employed seven spherical lens powers, from -3 to +3 diopters, in successive runs on two human subjects with corrected-to-normal vision. Each contrast sensitivity measurement necessitated less than a minute of eye tracking data. We derived contrast thresholds by analyzing the positional errors between the target stimulus and the subjects' gaze positions. A 95% confidence interval was obtained by projecting a moving confidence interval about the positional error onto the decreasing stimulus contrast function. A plot of contrast threshold vs. lens power showed a clear dependence on positive diopter values and a shallow dependence on negative ones, likely due to partial compensation from accommodation. We found that each subject’s optimal lens power coincided with their previously measured corrected-to-normal vision. Our findings demonstrate the utility of continuous psychophysics integrated with eye tracking for more ecologically valid measurements of contrast sensitivity and refractive errors. This method could be used for clinically challenging human populations, and could be adapted for non-human primates such as marmosets or macaques, extensively used in vision research, thereby eliminating the need for anesthesia in retinoscopy or prolonged behavioral training and testing.

Disclosures: **E.S. Pirso:** None. **J.F. Mitchell:** None. **C. Baker:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.01/Web Only

Topic: D.06. Vision

Title: Average Sound Level can be Extracted from Visual Scene Ensembles without Reliance on Color

Authors: *V. THARMARATNAM, D. B. WALTHER, J. S. CANT;
Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Due to inherent limitations in working memory and attention, our brains are not able to process all the abundant sensory information around us. In response, human brains make rapid and accurate ‘gist’ estimates of groups of visual items (i.e., visual ensembles) to compress redundant information. For example, in a fraction of a second and without reliance on visual

working memory (VWM), humans can accurately extract visual statistics from ensembles of objects and faces, such as average orientation and emotion, respectively. Recently, Tharmaratnam and colleagues (VSS 2019) demonstrated that ensemble statistics can be extracted from more complex stimuli like groups of scenes. Namely, average scene content (i.e., how natural or manufactured scenes look on average) and spatial boundary (i.e., how open or closed scenes look on average) can be extracted. Furthermore, Jung and Walther (2021) have shown that non-visual multisensory attributes (i.e., apparent sound level: how quiet or loud a scene would feel) of single scenes are represented in the prefrontal cortex and are accurately rated by observers. Given the flexibility of ensemble encoding, we examined if sound level summary statistics could be extracted by human participants, and whether lower-level features like color mediated this process. Participants rated the average sound level of scene ensembles, with either colored (Exp. 1, N=38, 12 male) or gray-scaled stimuli (Exp. 2, N=19, 6 male). Set-sizes of 1, 2, 4, or 6 scenes were presented on each trial, and VWM capacity was measured using a 2-AFC task. Participants were able to accurately extract average sound level in both experiments, with all 6 scenes being integrated into their summary statistics, yet less than 1.2 scenes were remembered on average. These results reveal that ensemble processing can compress cross-modal information from complex scene stimuli, and does not rely on colour to do so. These results will help explain a universal mechanism by which the brain mitigates sensory overload. This is vital because how we perceive the world impacts how we think. For example, an inability to mitigate sensory overload has been correlated with neurological disorders such as schizophrenia and autism.

Disclosures: V. Tharmaratnam: None. **D.B. Walther:** None. **J.S. Cant:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.02

Topic: D.06. Vision

Title: Prototypical representation of scenes: Evidence of memory distortion along the vertical axis and its neural mechanism

Authors: *Y. WU[1,2,3], S. LI[1,2,3];
[1]Sch. of Psychological and Cognitive Sci., Peking Univ., Beijing, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [3]Beijing Key Lab. of Behavior and Mental Hlth., Beijing, China

Abstract: Scene memory is prone to systematic distortions that could arise from the experience with external world. Understanding this adaptive phenomenon may provide new insights into the mechanism of scene processing. A well-known distortion along the near-far axis of the three-dimensional space, called boundary transformation, demonstrates the observer's erroneous recall of the viewing distance of scenes. The investigators argued for the role of the normalization

process to the high-probability prototypical viewing distance in boundary transformation. Here, we hypothesized that vertical angle of view (AOV) constitutes a prototypical viewpoint due to the varied vertical layouts of scenes and may cause memory distortion along the vertical axis of scenes. In a behavioral task (n = 79), we found a systematic memory distortion in AOV toward either the upper or lower field of the scenes. Computational modeling suggests that the AOV biases could be jointly predicted by the complexity information of the scenes and the independent subjective AOV ratings from a large set of online participants (n = 1208). We further conducted a functional magnetic resonance imaging (fMRI) experiment and a magnetoencephalography (MEG) experiment to investigate the neural mechanism behind the observed behavioral effects of memory distortion. The results of the fMRI experiment (n = 24) provided neural evidence that intermediate visual processing area (V4) may convey the complexity information and transfer it to scene selective areas, serving as the perceptual input to the normalization process. The results of the MEG experiment (n = 14) revealed an early representation of complexity information around 200 ms after scene onset and a late representation of memory distortion around 400 ms after scene onset. Furthermore, we observed stronger frontal theta power and weaker posterior alpha power when AOV bias occurred. Together, these findings suggest that the normalization process based on prototypical viewpoints is fundamental in scene processing. The normalization process involved a feedforward process of complexity from the intermediate level of visual pathway and a feedback process that conveyed the influence of prototypical viewpoints in the late stage of scene processing.

Disclosures: **Y. Wu:** None. **S. Li:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.03/W12

Topic: D.06. Vision

Support: BBSRC: BB/V003917/1

Title: The bilateral involvement of lateral occipital regions in shape processing

Authors: *J. A. TEED, C. L. SCRIVENER, R. D. MCINTOSH, E. H. SILSON;
Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: In 2011 Konen et al., presented a case study of patient SM; a stroke patient with a right lateralised lesion located between the dorsal and ventral banks of retinotopic maps, resulting in object agnosia. Functional magnetic resonance imaging (fMRI) revealed decreases in object-selective activity in the region surrounding the lesion in the right hemisphere and the homologous site in the intact left hemisphere, suggesting a right lateralisation of object processing. Previous research has shown object responses are more concentrated in retinotopic LO2 (Larsson & Heeger, 2006; Silson et al., 2013), yet SM exhibited typical levels of object

responsivity across early bilateral retinotopic cortex. To explore the contribution of the cortical region of SM's lesion to object processing, we performed participant-level univariate analysis of shape-responsive and object-selective fMRI data in neurotypical participants. Bilateral shape activation was found ventral to LO2 in both hemispheres between the dorsal and ventral banks of retinotopic maps in a commensurate location to SM's lesion. This cortical area was independently verified as object-selective by overlaying the shape-responsive region of interest (ROI) over object > scrambled object contrasts. Individual variation was present in the neural locus of peak shape responsivity bilaterally in this correspondent lesion location. However, a paired samples t-test revealed no significant difference between average shape related activation across hemispheres in each ROI. These results reveal the distribution of shape representation in ventral visual areas within and between hemispheres. Further confirmatory work will distinguish the role of these homologous regions across hemispheres in shape processing. This goal can be achieved by disrupting neural activity in each hemisphere using transcranial magnetic stimulation (TMS) and observing the relative effects on shape discrimination performance.

Disclosures: J.A. Teed: None. **C.L. Scrivener:** None. **R.D. McIntosh:** None. **E.H. Silson:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.04/W13

Topic: D.06. Vision

Support: T32 Grant MH064913-20
Vanderbilt Internal IDD Reads Grant

Title: Evaluating image quality and category representativeness in popular image sets: a path towards improved computer vision, cognitive models, and multimodal datasets

Authors: *W. J. QUACKENBUSH[1], M. T. WALLACE[2], D. A. TOVAR[2];
[1]Vanderbilt Brain Inst., [2]Psychology, Vanderbilt Univ., Nashville, TN

Abstract: The fields of computer vision and neuroscience have often made use of extensive image datasets. These datasets, collected via laborious web scraping efforts, have often prioritized quantity over quality, leading to uneven representations across categories. This inequality ostensibly may affect computer vision models, neuroscience findings, as well as studies that attempt to bridge computer vision and neuroscience. In the current study, we evaluated the extent by which image quality issues and image inconsistencies affect popular existing image sets. We first characterized image quality using well-known reference and non-reference image quality metrics for all object categories. We found differences in image quality across categories for all datasets analyzed. According to the perceptual-based image quality evaluator (PIQUE), a metric that indicates increased image quality with a lower score, an

ImageNet category with lower image quality is ‘website’ (M = 60.0039, SD = 9.9928), while a higher image quality category is ‘scuba diver’ (M = 24.9626, SD = 9.3722). A category representativeness metric was then generated using ImageBind, an AI model capable of binding six different modalities, including text and image embeddings, within a shared embedding space. To validate the neural and perceptual validity of ImageBind text embeddings, we examined their correlations with neural data of participants viewing various Snodgrass drawings. The significant correspondence ($p < 0.001$) between brain data and ImageBind text embeddings showed that the embeddings were perceptually valid. We then used ImageBind’s textual embeddings to assess how well object categories (concept embeddings) corresponded with images (visual embeddings). The degree to which conceptual text embeddings and visual embeddings matched differentiated the representativeness of object to concept, with higher embeddings values indicating increased correspondence. For example, the ImageNet textual embedding ‘spotted salamander’ (M = 35.96829) was well represented by its images, while the embedding ‘Cardigan Welsh Corgi’ (M = 11.374852) was not. By leveraging the multimodal embedding space of ImageBind coupled with ongoing generative AI efforts, our findings not only shed light on the pressing need for improvements in current datasets but also provide motivation for the immense potential generative stimuli may provide. Furthermore, we provide a methodological foundation for consistent, high-quality, and representative stimulus sets, and our framework is amenable to the evolution of future multimodal datasets, advancing the field of computer vision and neuroscience.

Disclosures: **W.J. Quackenbush:** None. **M.T. Wallace:** None. **D.A. Tovar:** A. Employment/Salary (full or part-time):; Meta.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.05/W14

Topic: D.06. Vision

Support: Vision Science to Applications (VISTA) program
Canada First Research Excellence Fund (CFREF, 2016–2023)
Discovery Grant from the Natural Sciences and Engineering Research Council of Canada

Title: Brain Responses to Symmetries in Naturalistic Novel Three Dimensional Objects

Authors: ***S. RAGAVALOO**, P. J. KOHLER;
Psychology, York Univ., Toronto, ON, Canada

Abstract: Symmetries are prevalent in natural and man-made objects and scenes. During natural vision, symmetries in the world are subject to perspective distortions and rarely produce symmetrical images on the retina. In this exploratory study, we investigated the ability of the

human visual system to overcome distortions when responding to symmetries in the world, by using high density EEG to measure responses to symmetries in naturalistic, novel three dimensional (3D) objects. We used a Steady State Visual Evoked Potentials (SSVEPs) paradigm to isolate EEG signals associated with symmetry processing.We presented images of symmetrical objects paired with images of asymmetrical objects under two conditions: One where images were rendered to produce symmetries in the image plane, and another where the objects were rotated relative to viewing direction such that symmetries in the object would be distorted in the resulting image. We selected image pairs that were matched on non-symmetry related features based on activations in an artificial neural network. The two images in a pair were shown one after the other, each for 500ms, to form a stimulus cycle (stimulation frequency=1 Hz). For both conditions, we created control conditions where the objects never had symmetry. Participants (n=30) passively viewed 10 such cycles per trial, with 10 unique image pairs. A follow up experiment (n=30) followed the same design but used images in which the shading cues to 3D object shape had been removed to create 2D object images.Previous studies have found that distorted symmetries in dot patterns elicits symmetry responses only when participants are engaged in symmetry related tasks. We find that image level symmetry elicits strong and broad responses suggesting occipital and temporal cortical sources. Perspective distorted symmetry also elicits strong responses, but they are weaker in posterior locations and more right lateralized. The 2D versions of the image level symmetry stimuli elicit similar responses to 3D. Removing cues to 3D shape eliminates symmetry responses from perspective distorted stimuli, serving as a manipulation check.Our results show that during passive viewing, perspective distorted symmetry can elicit SSVEPs that are comparable to those elicited by image level symmetry, but more strongly right lateralized and only in regions likely driven by activity in higher level visual cortex. Future work will determine how task and viewing conditions influence responses. This work was supported by the Canada First Research Excellence Fund and by a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada awarded to P.J.K.

Disclosures: S. Ragavaloo: None. **P.J. Kohler:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

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Program #/Poster #: PSTR083.06/W15

Topic: D.06. Vision

Support: SFARI 514755.5000.P01483.487

Title: Inverted visual coding at the cortical apex in autism

Authors: *A. STEEL[1], E. H. SILSON[2], B. D. GARCIA[1], C. ROBERTSON[1];
[1]Dartmouth Col., Hanover, NH; [2]Psychology, Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: We encode the world retinotopically, imparting a spatial code on visual information processing. Classic theories of cortical functional organization propose that this retinotopic code is replaced by abstract, amodal coding as information propagates through the visual hierarchy towards memory areas at the cortical apex, like the default mode network. However, recent work from our lab (Steel et al., 2023, bioRxiv) and others (Szinte & Knapen, 2020, Cerebral Cortex; Klink et al., 2021 eLife) suggests that retinotopic coding persists in mnemonic cortex at the cortical apex, and, intriguingly, that a large portion of the pRFs in mnemonic cortex have inverted visual response amplitudes. The inversion of the visual response amplitude suggests a possible role for inhibition (either feedforward or local inhibitory processes) in visual coding within memory areas. Here, we asked whether these negative population receptive fields (negative pRFs) were similarly distributed in participants with autism spectrum condition. We performed population receptive field mapping in 10 male and female participants with autism and a set of matched control participants. We found widespread, robust visual coding in the autistic participants, including inverted visual coding (i.e., negative pRFs) in lateral parietal and anterior medial ventral temporal cortex. Across the brain, the distribution of negative pRFs in autism was similar to the control population: negative pRFs emerged anterior to visual areas and were largely restricted to the default mode network. Analysis of individualized functional localizers revealed that negative pRFs were concentrated within swaths of cortex that selectively activated when participants visually recalled personally familiar places (versus people). In contrast with areas involved in place memory recall, negative pRFs were largely absent from scene-selective perceptual areas in both controls and participants with autism. These results show that inverted visual coding is a consistent feature of cortical function and is readily observable in this neurodivergent population. Further work will consider the role of inhibition in establishing negative pRFs, as well as the functional role that this inverted visual code might play in cognition.

Disclosures: **A. Steel:** None. **E.H. Silson:** None. **B.D. Garcia:** None. **C. Robertson:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.07/W16

Topic: D.06. Vision

Support: NRF-2022R1A2C3008991
NRF-2021M3E5D2A01019544
NRF-2019M3E5D2A01058328

Title: Emergence of aesthetic preferences in untrained deep neural networks

Authors: *H. LEE[1], S.-B. PAIK[2];
[1]Bio and Brain Engin., [2]Brain and Cognitive Sci., KAIST, Daejeon, Korea, Republic of

Abstract: The ability to estimate the ratio between two visual magnitudes is essential during animal activities for survival, such as hunting, foraging, and mating (Jacob 2012). For example, a group of animals judges whether or not to attack an opponent group based on the relative size of the population (McComb 1994, Wilson 2002). Intriguingly, behavioral studies have also found that a certain visual ratio value plays an important role in aesthetic judgements — visually pleasing artworks, faces, and patterns are known to be structured with a particular ratio value, termed the golden ratio (Di 2007, Jacob 2012). Previous studies have also reported that neural activities selective to the golden ratio in artworks have been observed in the brain and are thus considered as a neural basis of aesthetic judgement (Di 2007, Noguchi 2013). However, how the brain can develop such neural tuning remains unclear. One notable characteristic of the golden ratio is the link to the Fibonacci sequence, in which each number is the sum of the two preceding numbers. As the Fibonacci sequence progresses, the ratio between consecutive numbers approaches the golden ratio. With this notion, here we show that selectivity to the golden ratio may arise spontaneously from simple feedforward wirings in hierarchical neural networks. Specifically, if there are neurons selective to each Fibonacci number in hierarchical layers (F_n, F_{n+1}), the corresponding feedforward projections can generate neural selectivity to the subsequent Fibonacci number (F_{n+2}) and, eventually, tuning to the ratio between Fibonacci numbers (F_n/F_{n+1}). Using a brain-inspired model neural network, we found that single neurons tuned to the golden ratio between two continuous line lengths can arise spontaneously in untrained neural networks. We confirmed that these neurons exhibit robust selectivity to their preferred proportions, regardless of the absolute length of each line, and that they are more prevalent in deep layers of hierarchical networks. These units enable the network to perform a task so as to determine whether or not a given stimulus represents the golden ratio, which may allow aesthetic judgements. These results collectively suggest that single neuronal tunings for various cognitive functions, including neural tuning to aesthetic parameters, can emerge spontaneously in untrained neural networks, providing insight into the developmental mechanisms of innate cognitive functions.

Disclosures: H. Lee: None. **S. Paik:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.08/W17

Topic: D.06. Vision

Support: No. 2021R1G1A1092988
Chunbuk National University Research Support program

Title: Consistency of visual memorability across cultures

Authors: *Y. LEE, S. K. JEONG;
Chungbuk Natl. Univ., Cheongju-si, Korea, Republic of

Abstract: Memorability refers to an inherent quality of a stimulus that determines how well it is remembered or forgotten. Recent research has discovered that memorability remains remarkably consistent among and across individuals. Previous memorability studies have primarily focused on participants from Western cultures and implicitly assumed that memorability would be culturally consistent. However, to the best of our knowledge, this has not yet been empirically investigated. In the current study, we recruited participants from South Korea and the United States to explore cross-cultural consistency in image memorability. The results across several experiments showed no significant differences in the correlation between the memory performance of U.S. participants, the memory performance of Korean participants, and the memorability scores in the image database. Moreover, South Korean participants demonstrated slightly better memory performance for images rated as highly memorable by U.S. participants. These findings provide converging evidence that individual differences do not entirely explain visual memorability and further suggest the possibility of cross-cultural consistency in visual memorability.

Disclosures: **Y. Lee:** None. **S.K. Jeong:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.09/W18

Topic: D.06. Vision

Support: National Institute of Neurological Disorders and Stroke (NS116623)
National Eye Institute (EY014924)
National Eye Institute (EY029759)

Title: Border ownership selectivity and laminar connectivity in single columns of macaque V1 measured with high density Neuropixels recordings

Authors: *S. ZHU[1], Y. OH[1], E. TREPKA[1], X. CHEN[2], T. MOORE[1];
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Abstract: It is known that stimulating the surround of a visual cortical neuron's classical receptive field (cRF) can modulate responses to stimuli presented inside the cRF. This property is essential for optimal coding and important visual perception, e.g. figure-ground segmentation. One example of contextual modulation is the encoding of border ownership (BOWN) in visual cortex, particularly in area V2, where many neurons signal the side to which an object's edge belongs. At present, it remains unclear to what extent neurons at earlier processing stages, particularly those across different layers in V1, signal border ownership. To address this question, we examined the responses of large populations of macaque V1 neurons to standard

BOWN test stimuli. Neuronal activity was recorded using high-density Neuropixels probes (Imec, Inc.). In each session (N = 8), Neuropixels recordings were largely confined to single V1 columns composed of neurons with similar orientation preferences and highly overlapping cRFs. BOWN test stimuli consisted of uniform luminance white or black objects (8º squares) on a black or white background, respectively. And one edge of the object fell within the cRFs of the neuronal population. BOWN selectivity was quantified as the difference in neuronal responses to edges with identical stimuli inside cRFs but belonging to opposite sides of the object determined by the surround at least 4º away from cRFs. We measured the degree to which populations of V1 neurons across layers could signal border ownership by testing the performance of a binary decoder in identifying the side to which the object's edge belonged. We found that the performance of the decoder exceeded the chance level for populations of neurons across all cortical layers with similar latency, suggesting that border ownership signals are present at the earliest stages of visual cortical processing. Next, we took advantage of high density recordings and identified 1000s of functionally interacting neuronal pairs using cross-correlation. Neuronal pairs were separated by their laminar locations. The same analysis was performed on another dataset that was collected at the same recording session, but with classical RF stimulation (drifting Gabor grating, 1.5º in diameter). We found that the laminar connectivity pattern differed between classical and non-classical stimulation conditions. Specifically, under BOWN stimuli presentation, we observed a significantly higher proportion of Layer 5/6 leading Layer 4c activity. This result is consistent with evidence suggesting that Layer 5/6 neurons generate contextual selectivity through feedback connections from higher visual areas.

Disclosures: S. Zhu: None. **Y. Oh:** None. **E. Trepka:** None. **X. Chen:** None. **T. Moore:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Program #/Poster #: PSTR083.10/W19

Topic: D.06. Vision

Support: HHMI

Title: How populations of neurons in visual cortex encode perspective

Authors: *J. HOELLER[1], L. ZHONG[1], M. PACHITARIU[2], S. ROMANI[1];
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Abstract: As we move around the world, we see the same visual scene from different perspectives. While our percept remains stable, most neuronal responses in visual cortex do not. This suggests that a variable representation in the visual cortex must be transformed into a perspective-invariant one before it is used for perception. Some theories propose that, in order to achieve perspective invariance, the variability in the visual cortical representation must be determined by the observer's spatial relationship to the scene, not by the scene itself. To test

these theories, we developed computational methods to analyze the variability in neuronal representations with perspective. We provide evidence in favor of theories of perspective invariance from large-scale calcium imaging data in awake mice.

Disclosures: **J. Hoeller:** None. **L. Zhong:** None. **M. Pachitariu:** None. **S. Romani:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.11/Web Only

Topic: D.06. Vision

Support: TUBITAK 1002 GRANT 122K706

Title: Perception of Built Environments and its Neural Modulation by the Behavioral Goals of the Perceiver

Authors: *A. KOÇ[1,3], B. A. URGEN[4,3,1], Y. AFACAN[2,1];
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Abstract: A scene refers to a view of an environment with a spatial layout one can act within. Scenes have been studied extensively in the neuroscience literature, including changes in neural activity patterns, across the brain and scene-selective areas (PPA, RSC, OPA), in response to low to high-level features, categories, and content across various tasks. However, previous research has mainly focused on outdoor scenes and broad category differences (e.g. natural vs. man-made) or simple differences between otherwise similar indoor scenes (e.g. scale), with tasks that are either category-related or irrelevant to the stimuli. Interactions with fields such as environmental psychology or neuroarchitecture, which could inspire an ecologically valid study of scenes, have been limited. In this study, we look specifically at the perception of built environments where we spend most of our time, drew our categorization method from the architecture literature, and used multiple tasks. Our categories were (i) architectural elements that allow our access to and circulation within an environment (entrances, exits, stairs, elevators, and corridors); and (ii) functional areas that do not aid locomotion but respond to human needs (restrooms, eating and seating areas). Functional magnetic resonance imaging (fMRI) data were collected from 23 right-handed participants (12 females) while they were engaged in 2 different tasks as they viewed scenes from built environment categories: a categorization task based on the main afforded action differences between the categories we defined, and an approach-avoidance task where the participant decided to enter the scene or not, measuring the initial action regarding an environment. Regions of interest (ROIs) were determined using a separate localizer experiment. Whole-brain univariate analyses did not reveal strong differences between the tasks.

Searchlight MVPA revealed categories, but not tasks, are classified at the whole-brain level, at the lingual and parahippocampal gyri, the SMA, and the occipital cortex. Model-based representational similarity analysis (RSA) at the ROI level revealed that tasks modulate neural activation patterns to built environments in all three scene-selective regions, but do not entirely explain them, whereas categorical and visual models did not correlate with the neural activation patterns in any of the ROIs. We demonstrate an interdisciplinary approach to scene perception to expand the ecological validity of stimuli and task content and show that neural responses to built environments are modulated by the task at the ROI level, and category at the whole-brain level.

Disclosures: **A. Koç:** None. **B.A. Urgen:** None. **Y. Afacan:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Grant No. KJZD-SW-L08
Grant No. KJZD-SW-L08
Grant No.YSBR-071

Title: The nature and dynamics of the feedback signal to early visual cortex during peripheral object identification

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Abstract: Plenty of evidence has shown that the neural feedback signal is critical for object recognition in the visual system. However, the specific nature of the object information conveyed by these feedback signals remains elusive. Different object features are encoded at different stages of visual processing, but what kinds of feature information are sent back to early visual cortex and how do they interact with the feedforward process to facilitate object perception? Previous studies have shown that feedback information from peripherally presented objects is present in the foveal region of early visual cortex, providing a paradigm for dissociating feedback signals from feedforward signals. In the current study, a peripheral object identification task was used to examine the representation of two types of visual features in the feedback signals: the orientation information, which is originally encoded in the early visual cortex, and category information that is generated in high-level object processing cortex. Data from 18 participants (10 females, age 19-29) were collected with ultra-high-field MRI (7T), and data from 15 participants (10 females, age 19-29) were collected with magnetoencephalogram (MEG). Taking advantage of the high resolution of fMRI (0.8 mm isotropic), the laminar profiles

of both feedforward and feedback signals were examined in V1. The results showed that the orientation information was only fed back to the deep layer of foveal V1, whereas the category information was fed back to both the deep and superficial layers of foveal V1. The MEG data and source reconstruction analysis showed that the category information emerged earlier and sustained much longer than the orientation information in the feedback signals, and only the category feedback information was significantly relevant to the behavioral performance. Granger causality analysis showed that the category feedback information observed in the early visual cortex originated from the temporal lobe. Our results revealed the dominance of category information in the feedback information during peripheral object processing, suggesting that the neural feedback mechanism not only enhances the stimulus features originally encoded in the low-level cortex, but also communicates the complex representations generated in the high-level cortex to the low-level cortex to facilitate stimulus processing throughout the neural system.

Disclosures: **W. Hou:** None. **S. He:** None. **J. Zhang:** None.

Poster

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Title: Neural Networks Learn Object and Environmental Statistics to Guide Foraging Decisions

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Abstract: Foraging behavior is imperative to day-to-day life, requiring careful balance between exploration and exploitation, use of sensory cues to direct reward-seeking behavior, and mental mapping of the surrounding environment. The complexity of this behavior makes it difficult to generate hypotheses about neural mechanisms that are straightforward to test experimentally. We addressed this challenge by training a recurrent neural network (RNN) via reinforcement learning to complete a naturalistic foraging task. The RNN agent learned to pursue high value paths through its environment, demonstrating that it learned the correspondence between stimulus values and rewards, and statistics about the stimuli themselves. Furthermore, RNN agents trained on environments with different statistics, such as environments with zones containing different reward magnitudes or probabilities, adjusted their behavior accordingly. Our

results indicate that simple agents can use both statistics about the environment and stimuli to guide decision-making.
This model will generate hypotheses about interactions between reward-guided decision-making and visual processing. To make connections with responses of neurons in visual cortex, we are adjusting the model so that rather than receiving scalar inputs reflecting stimulus information, it will interpret the responses of a convolutional neural network (CNN) trained on image identification or recordings from groups of neurons in macaque V4. Our preliminary results suggest that the RNN can use CNN inputs to learn the statistics of the stimuli and can generalize to novel stimuli.
This modeling framework will allow us to generate and test hypotheses about the relationship between vision and decision-making. By separating decision-making from visual processing, we can examine the ability of each module to generalize learning to new stimuli and relative the efficiency of altering each module to learn new tasks. This work highlights the value of using simple models to generate hypotheses about the brain mechanisms that support complex cognitive processes.

Disclosures: **A.G. Orwant:** None. **R. Srinath:** None. **M.R. Cohen:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Topic: D.06. Vision

Support: BBSRC Grant BB/V003917/1

Title: Retinotopically informed computational models improve correspondence with responses in scene-selective brain regions

Authors: C. SCRIVENER[1], E. ZAMBONI[2], I. I. GROEN[3], A. B. MORLAND[2], ***E. H. SILSON**[1];
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Abstract: Image computable models, such as GIST (Oliva & Torralba, 2006), are commonly employed to aid interpretation of multivoxel patterns measured from the human brain. For instance, responses in scene-selective regions Occipital Place Area (OPA) and Parahippocampal Place Area (PPA) are both sensitive to low-level image manipulations of spatial frequency and correlate positively with GIST descriptors (Groen et al., 2013; Watson et al., 2014, 2016). However, the way brain areas and image computable models sample the visual world differ markedly. These models typically perform computations across the entire image, whereas the brain regions they are compared to do not evenly represent the visual field. For instance, OPA and PPA exhibit differential biases for the contralateral lower and upper visual fields,

respectively (Silson et al., 2015). Given this discrepancy in spatial sampling between brain regions and the models they are compared with, we asked a simple question: What happens to this correspondence if the inherent retinotopic profiles of the regions are considered? We measured population receptive fields, localised scene-selective regions of interest (i.e., OPA, PPA), and measured the multivoxel patterns elicited by 96 complex scenes in a slow event-related design in a group of 24 participants. We calculated the pairwise dissimilarity (*1-pearson's r, representational dissimilarity matrix)* between each scene and compared the neural RDMs for each ROI with three models: 1) GIST derived from the whole scenes, 2) GIST derived from scenes masked by each subject's visual field coverage for each ROI, and 3) GIST derived from scenes masked by the subject's visual field coverage and then rotated by 180 degrees. If the similarity between each ROIs neural RDM and the model RDMs reflects the underlying retinotopic profile of the ROI, then filtering the images by the coverage should either improve the correspondence between brain and model, or at least not reduce it. Moreover, rotating the image 180 degrees pre-filtering should result in a lower correlation than either the GIST or the filtered GIST models. Retinotopically filtered GIST descriptors better matched neural responses in OPA than either whole or rotated GIST descriptors and were equivalent to whole GIST descriptors in PPA. This result is remarkable considering that the retinotopically filtered GIST descriptors were computed over ~35% of the image on average. These data suggest that the responses to complex scenes in OPA and PPA reflect retinotopically specific visual information available to each region and highlights the need to account for retinotopy when making visual cortex-model comparisons.

Disclosures: C. Scrivener: None. **E. Zamboni:** None. **I.I. Groen:** None. **A.B. Morland:** None. **E.H. Silson:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Topic: D.06. Vision

Support: KU Leuven grant C14/22/134

Title: Neuronal tuning and population representations of shape and category in human visual cortex.

Authors: *P. JANSSEN[1], V. BOUGOU[1], M. VANHOYLAND[1], A. BERTRAND[1], H. OP DE BEECK[1], T. THEYS[2];
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Abstract: Object recognition and categorization are fundamental cognitive processes in the human ventral visual stream. However, the specific tuning properties of neurons in the ventral stream for object shape and category remain largely unknown. In this study, we conducted

invasive recordings using 96-channel microelectrode Utah-arrays in the Lateral Occipital Complex (LOC) of 3 neurosurgical patients (4 Utah-arrays). We analyzed multi-unit spiking activity (MUA), while presenting a stimulus set of 54 images in which shape and category were dissociated (Bracci S., Op de Beeck H., The Journal of Neuroscience, 2016). We employed two distinct analytical approaches: one at the single-channel level and one at the population level. At the single-channel level, we recorded from a total of 237 visually responsive MUA sites. Using 2-way ANOVA on the net MUA responses, we determined selectivity for shape, category, and any shape-category interactions. A significant interaction between shape type and category was observed in almost half of the channels (114 out of 237, 48%), compared to those selectively responsive to shape type alone (39 sites, 16%) or category alone (8 sites, 3%) ($chi2 = 143$, $p < 0.0001$). At the population level, multidimensional scaling analysis (MDS) revealed primarily shape representations in the neural space of all arrays. Next, we employed linear decoding to extract multidimensional information about shape type and category. Linear Support Vector Machines (SVMs) were trained on the neural responses per array (100 ms bins with a sliding window of 50 ms). We successfully decoded shape type starting as early as 75 ms after stimulus onset for array 1, 100 ms for array 2, and 200 ms for arrays 3 and 4. Notably, despite primarily representing shape type, significant category classification emerged simultaneously across all arrays, indicating that a population of shape-selective neurons in the human visual cortex contains reliable category information. Furthermore, we assessed the generalization of decoders over time by training shape and category decoders using 100 ms time windows and testing them on every 100 ms window that followed or preceded the training bin. While one array showed high decoding accuracy for both shape type and category throughout the stimulus duration, suggesting a stationary population representation early after stimulus onset, the other three arrays exhibited more transient generalization of the classifier. Our results represent the first detailed study on shape and category coding at the neuronal level in the human ventral visual stream, furnishing essential evidence that reconciles human imaging and macaque single-cell studies.

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Poster

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Topic: D.06. Vision

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Title: The interaction between internal and external attention depends on predictability

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Abstract: Whereas external attention selects perceptual information, the selection of internal attention is based on the internal representation in memory. Previous research has demonstrated that the external and internal attention interact with each other. However, a recent study (Lim & Pratt, 2023) reported that the breadth of the internal attentional window does not impact the processing of external perceptual stimuli. In the previous study, internal attention was influenced by varying the size of the working memory array, while external attention was manipulated using different sizes of flanker arrays during task performance. The results revealed that the overlap between internal and external attentional windows did not significantly affect participants' performance on the flanker task. However, in the previous study, the size of internal and external attentional windows varied on a trial-to-trial basis, potentially limiting participants' ability to flexibly adjust their attentional window size. Therefore, the current study investigated whether the size of the internal attentional window affects external attention in a flanker task when the attentional window size is predictable. We adopted the experimental paradigm of Lim and Pratt (2023) but kept the size of the internal and external attention window consistent within a block. In contrast to the previous study, our findings demonstrated that the processing of flankers was disrupted when they fell within the breadth of the internal attentional window, but only when the size of the attentional window was predictable. These findings suggest that internal and external attention interact with each other when top-down knowledge of the task context is available.

Disclosures: Y. Kim: None. **S.K. Jeong:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Topic: D.06. Vision

Support: STI2030-Major Projects 2021ZD0200200

Title: Object color knowledge representation in the macaque brain

Authors: *M. ZHAO[1,2], Y. XIN[1,2], H. DENG[1,2], Z. ZUO[1,2], X. WANG[3,4], Y. BI[3,4], N. LIU[1,2]; [1]Chinese Acad. of Sci., Beijing, China; [2]Inst. of Biophysics, Beijing, China; [3]IDG/McGovern Inst. for Brain Res., [4]Beijing Key Lab. of Brain Imaging and Connectomics, Beijing Normal Univ., Beijing, China

Abstract: Animals guide their behaviors through internal representations of the world in the brain. We aimed to understand how the macaque brain stores such general world knowledge, focusing on object color and related integrative knowledge. By conducting three functional magnetic resonance imaging (fMRI) experiments (i.e., color perception, grayscale object viewing, true- and false-colored object viewing), we observed a distributed pattern of object knowledge representations. One type is grounded in color perceptual experiences, stored in the color patches located in ventral V4 (V4v) and inferotemporal (IT) cortex (PITd, near the dorsal

posterior inferior temporal area; PLc, posterior lateral color patch; ALc, anterior lateral color patch), where brain activity patterns could decode the typical colors of fruits and vegetables presented as grayscale pictures; and another is in the temporal pole (TP), which showed stronger responses to true- than false-colored objects but could not decode memory colors of grayscale object images, storing integrative object information that is abstracted away from specific sensory properties. These results indicate the perceptually grounded knowledge representation as a conservative memory mechanism and open a new avenue to study the conservative and potentially human-specific semantic memory representations with macaque models.

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Poster

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Topic: D.06. Vision

Support: Krieger Mind/Brain Institute

Title: A visuo-haptic experimental setup for exploring 3D-shape representation in macaque inferotemporal cortex

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Abstract: We use our senses of vision and touch to explore the 3D shape of objects in our environment, but little is known about how the brain integrates shape information from these two distinct senses. Human fMRI studies point to the lateral occipital complex (LOC) as a potential site of visuo-haptic shape integration. To investigate visuo-haptic shape representation at the level of individual neurons, we aim to conduct electrophysiological recordings in macaque inferotemporal cortex (IT), the putative homologue of LOC. Towards this aim, we have developed a visuo-haptic experimental setup in which 3D shapes are presented to macaques haptically and visually. For haptic stimulus presentations, objects are selected from a library of ~850 3D-printed stimuli and are delivered by a robotic manipulator to the macaque. Because the robotic manipulator can present objects in multiple orientations, the virtual size of the stimulus set is multiplied, thereby allowing a broader exploration of shape space. A network of high-speed cameras records the positions of the hand during grasping, allowing reconstruction of hand conformation and points of hand-object contact over time. For visual stimuli, a monitor displays realistic, high-resolution images of objects that exactly match the size and position of haptic stimuli.

Disclosures: **W.G. Snider:** None. **C.E. Connor:** None. **D.H. O'Connor:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Topic: D.06. Vision

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David and Lucile Packard Foundation

Title: Artificial neural networks dissociate features across positive and negative weights

Authors: *G. RAMOS-TRASLOSHEROS, C. R. PONCE;
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Abstract: In the primate, visual object recognition is associated with activity in the ventral stream, which terminates in inferotemporal cortex (IT). To model how the preferred high-level image features in IT depend on major input areas such as V4, we did ablation experiments in artificial neural networks (ANNs) trained for image classification (e.g., convolutional neural networks or CNNs). CNNs are the best models for hierarchical information processing in the ventral visual stream that have localized receptive fields. The image features encoded by individual units or populations can be identified using highly activating images. To efficiently find these images for each unit, we used generative neural networks combined with an evolutionary optimization algorithm. This method is gradient-free, so it can be used in closed-loop recordings both in vivo and with ANNs. We studied different ANNs, all (pre)trained on ImageNet, such as AlexNet, and ResNet50 (of varying adversarial robustness). For a given unit in an ANN layer, we investigated how its highly activating images changed after input weight ablation. Specifically, we ablated input weights from strongest to weakest in absolute value, under three conditions: (1) ablating only positive weights, (2) only negative weights, or (3) both. We found that the maximum response of units decreased with increasing proportions of ablated weights, this was true for the positive- and mixed-weight condition, but not under the negative-weight condition. To quantify the high-level visual similarity of the preferred images of a unit before and after ablation, we used an ensemble of different classification-trained ANNs and correlated their output activations between the control- vs. ablated-input images. We found that, despite eliciting different responses of the recorded units, the preferred images of the ablated-input units were similar to the preferred images of the intact units, even when ablating large fractions of each weight type. This resilience of ANN units was greater during the ablation of negative weights than during ablation of positive weights. This preliminary work shows that CNNs distribute different image features across positive vs. negative input weights. Further, this result was similar across different architectures and training (e.g., adversarial robustness). This suggests that there may be key differences in the contributions of excitatory vs. inhibitory neurons to IT neurons.

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Poster

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Program #/Poster #: PSTR083.20/W28

Topic: D.06. Vision

Support: Y81HN13701

Title: High-dimensional topographic organization of visual features in the primate temporal lobe

Authors: ***M. YAO**[1], B. WEN[1], M. YANG[1], J. GUO[1], H. JIANG[1], C. FENG[1], Y. CAO[1], H. HE[2], L. CHANG[1];
[1]Inst. of Neuroscience, Key Lab. of Primate Neurobiology, CAS Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China; [2]Inst. of Automation, Chinese Acad. of Sci., Beijing, China

Abstract: The inferotemporal cortex supports our supreme object recognition ability. Numerous studies have been conducted to elucidate the functional organization of this brain area, but there are still important questions that remain unanswered, including how this organization differs between humans and non-human primates. Here, we used a deep neural network trained on object categorization to construct a 25-dimensional space of visual features, and systematically measured the spatial organization of feature preference in both monkey brains and human brains using fMRI. These feature maps allowed us to predict the neural tuning of a previously unknown region, featuring the presence of objects with fine textures. This prediction was corroborated by additional fMRI and electrophysiological experiments. These maps also enable quantitative analyses of the topographic organization of the temporal lobe, demonstrating the co-existence of multiple functional gradients that differ in orientation and spatial scale, and revealing significant differences in the functional organization of high-level visual areas between monkey and human brains.

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Poster

PSTR083. Representation of Objects and Scenes

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.21/X1

Topic: D.06. Vision

Title: Investigating the capacity for tree shrew high-level vision

Authors: *E. E. MEYER, C. SONG, W. S. ONG, M. ARCARO;
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Abstract: A hallmark of primate vision is the ability to quickly and effortlessly recognize objects in our environment despite variation in how a single object may be projected on the retina. However, it remains unclear to what extent non-primate species share this ability (Vinken & Op de Beeck, 2021). Tree shrews (Tupaia belangeri), being one of the closest living relatives to primates, are a promising model for studying high-level vision. Similar to primates, tree shrews have an extensive extrastriate cortex that may support abstract object representations, although behavioral evidence is limited. Here we evaluated their ability to recognize objects across identity-preserving transformations and employed computational modeling techniques to assess the level of abstraction necessary to reproduce tree shrew behavior.

Three adult tree shrews were trained on a match-to-sample task, where they learned to visually discriminate objects that varied in position, size, and orientation. The shape similarity of targets and distractors, as well as background complexity (mean gray and natural scenes), varied across trials and sessions. Tree shrews were able to identify target objects across transformations even when they were embedded within complex scenes. Moreover, the patterns of behavioral performance were correlated across shrews, indicating that they utilize a common shape representation supporting object perception.

To gain deeper insight into the underlying representations driving their behavior, we compared the tree shrews' performance with predictions derived from models of retinal filtering and hierarchical processing. We adapted the Image System Engineering Toolbox for Biology (ISETBio) toolbox to simulate retinal processing based on the properties of the tree shrew eye. Although a linear readout of cone activations in response to the object images was sufficient for discriminating some target-distractor pairs above chance, these retinal representations did not capture the pattern of tree shrew behavior. To assess the level of abstraction beyond retinal processing required to account for the tree shrews' visual behavior, we are modeling representations at later processing stages using pre-trained convolutional deep neural networks (DNNs). At each layer, a linear readout of target-distractor discriminability is correlated with tree shrew behavior, providing insight into the depth of processing tree shrews employ in object recognition tasks.

These findings help establish tree shrews as a model for investigating high-level processing and offer insights into the unique and shared features of primate object recognition behavior.

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Poster

PSTR083. Representation of Objects and Scenes

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Title: High density recordings in macaque V2 reveal large clusters for shape and texture encoding

Authors: *R. S. KAMATH[1,2], K. KERR[2], T. KIM[2], T. NAMIMA[3,4,2,5], G. HATANAKA[2], W. BAIR[2,5], A. PASUPATHY[2,5];
[1]Univ. of Washington Grad. Program In Neurosci., Seattle, WA; [2]Biol. Structure, Univ. of Washington, Seattle, WA; [3]Osaka Univ., Suita, Japan; [4]Ctr. for Information and Neural Networks, Suita, Japan; [5]Washington Natl. Primate Res. Ctr., Seattle, WA

Abstract: Macaque cortical area V2 is an early stage of visual processing and includes neurons that show strong selectivity for stimulus form and surface texture. Whether this selectivity is functionally organized across laminae, such as in the orientation columns seen in V1, remains an open question. Using high-density Neuropixels probes in two anesthetized monkeys, we studied the responses of dozens of neurons simultaneously to different shape and texture stimuli. The shape set included between 15 and 50 simple closed 2D shapes that have previously been used in studies of shape selectivity, and were either darker, brighter, or equiluminant to the background. The textures included 40 naturalistic grayscale textures, and were either presented in their original form, in contrast-reversed form, or as a spectrally matched noise image synthesized from the original. All stimuli were centered on an aggregate receptive field (RF) of the population of neurons under study. Shape stimuli were sized to lie entirely within this RF, while texture stimuli were sized to cover the entire RF. Tuning similarity of the shape responses was strongly shared across nearby neurons, and the similarity drastically declined with inter-neuron distance. For responses to texture, tuning similarity between nearby neurons was moderate, and was shared across a greater distance of neurons. Roughly 55% (for shape) and 38% (for texture) of neurons exhibited tuning similarity that declined with increasing inter-neuron distance. We conclude that functional organization in V2 may be at a fine scale for shape and texture stimuli, with large clusters of similarly tuned neurons located together across laminae. These results are strikingly different from those we found in area V4, where clusters were sporadic and only ~20% of neurons exhibited similar shape/texture tuning with their neighbors in experiments with stimuli identical to those used here. These differences may relate to the convergence of a greater variety of inputs and the higher dimensionality of tuning in V4.

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Poster

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Title: Prefrontal cortex modulates V4 shape selectivity through inhibitory feedback

Authors: *T. KIM, E. KEMPKES, S. BEAUFRAND, A. PASUPATHY;
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Abstract: Macaque area V4, located along the ventral visual pathway, plays a crucial role in processing object shape. When an object is partially occluded, shape-selective neurons in V4 typically show reduced responses due to the loss of visual information. In contrast, neurons in the prefrontal cortex (PFC) exhibit heightened responses specifically to occluded shapes, suggesting their involvement in integrating contextual information to compensate for missing parts of occluded shapes. These mechanisms likely involve feedback transmission from PFC to V4 and contribute to the increase of V4 neuron's shape selectivity during the later phase of response dynamics. However, the przxecise nature of this interaction between PFC and V4 has not been dissected. In this study, we used Neuropixel probes to simultaneously record the activity of V4 and PFC neurons while an awake monkey was actively engaged in a task to discriminate the shape of occluded objects. To examine the influence of PFC on V4, we used cortical cooling to reversibly inactivate PFC. Our preliminary findings reveal distinct effects of cooling on PFC and V4. In PFC, approximately 65% of recorded neurons showed a significant correlation between the cooling temperature and response magnitude. Most of these neurons exhibited decreased activity during the cooling period. In V4, which was not directly cooled, a smaller proportion (38%) of neurons showed a significant correlation between PFC cooling temperature and response magnitude. Interestingly, the majority of these V4 neurons displayed increased activity during the cooling period. Further analysis of spike waveforms and cross-correlograms demonstrated that the observed mono-synaptic connections between PFC neurons predominantly originated from excitatory neurons in upper layers and targeted inhibitory (e.g., narrow-spiking) neurons in deeper layers. Taken together, our results suggest that PFC exerts inhibitory feedback on V4 activity, and the release of this inhibition during the cooling period leads to an augmentation of V4 activity. These findings provide valuable insights into the intricate interplay between PFC and V4 during the processing of occluded object shapes.

Disclosures: T. Kim: None. **E. Kempkes:** None. **S. Beaufrand:** None. **A. Pasupathy:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.24/X4

Topic: D.06. Vision

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Title: High-density recording reveals sparse clusters (but not columns) for shape and texture encoding in macaque V4

Authors: *T. NAMIMA[1,2,3,5], E. KEMPKES[3,5], P. ZAMARASHKINA[3,5], N. OWEN[4], A. PASUPATHY[3,5];
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Abstract: Macaque area V4 includes neurons that exhibit exquisite selectivity for visual form and surface texture, but their functional organization across laminae is unknown. We used high-density Neuropixels probes in two awake monkeys to characterize shape and texture tuning of dozens of neurons simultaneously across layers. We found sporadic clusters of neurons that exhibit similar tuning for shape and texture: ~20% exhibited similar tuning with their neighbors. Importantly, these clusters were confined to a few layers, seldom ‘columnar’ in structure. This was the case even when neurons were strongly driven, and exhibited robust contrast invariance for shape and texture tuning. We conclude that functional organization in area V4 is not columnar for shape or texture stimulus features. More broadly, these results support the hypothesis that cortical columns, rather than representing functional units, emerge as a result of representational expansion of afferent inputs, e.g. retina to V1 in the macaque. In V4 and other brain regions where afferents with heterogeneous tuning converge onto individual neurons, columnar structure may not be the norm.

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Poster

PSTR083. Representation of Objects and Scenes

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.25/X5

Topic: D.06. Vision

Support: NEI grant R01 EY018839 to AP
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Vision Core Grant P30EY01730 to UW
Office of Research Infrastructure Programs Grant OD010425 to the Washington National Primate Research

Title: Dynamics of a perceptual decision across visual and frontal cortex during shape discrimination under occlusion

Authors: E. KEMPKES[1], A. BIGELOW[2], ***A. PASUPATHY**[3];
[1]Biol. Structure, [2]Univ. of Washington, Seattle, WA; [3]Univ. Washington, Seattle, WA

Abstract: Successful recognition of partially occluded objects is presumed to involve dynamic interactions between brain areas responsible for vision and cognition. Based on recordings in monkeys performing a shape discrimination task under partial occlusion, we previously hypothesized that feedback from prefrontal cortex (PFC) to visual area V4 clarifies occluded object representations in V4 and facilitates shape discrimination (Fyall et al., 2017). But because these experiments were sequentially conducted, we do not know the dynamical interplay between the two areas. Here we conduct paired recordings in V4 and PFC using high-density Neuropixels probes, and perturb PFC activity by cooling, to delineate the dynamics of sensory and decision signals in the two brain areas.
Animals were trained to report whether two stimuli presented in sequence were the same or different via a saccade. The second stimulus in the sequence moved behind an occluding window centered on the RF of recorded V4 neurons. The occluding window included slits of varying width to titrate difficulty and animal performance. Unoccluded trials were also included. As the animal performed the task, we studied the responses of dozens of neurons simultaneously in V4 and PFC with a high-density Neuropixels probe inserted into each brain region. To perturb PFC activity we used a custom-designed cooling probe that modulated the temperature of the underlying cortex. We used targeted dimensionality reduction (Mante et al., 2013) to delineate the dynamics of shape, motion direction and occlusion information in the two areas, and capture the emergence of a decision signal.
On unoccluded trials we found earlier and stronger encoding of shape information in V4 and simultaneous emergence of decision signals in the two areas. On occluded trials, a short-lived occlusion selective signal emerged first followed by a bimodal shape selective signal in V4 and a unimodal signal in the PFC that peaked precisely between the two peaks in V4. The strongest sensory signal in both areas, however, encoded motion direction, and this signal emerged later and lasted longer on occluded trials. While this may seem irrelevant to the performance of the task, it may be critical for deriving the shape of a dynamic target. When PFC activity was perturbed, V4 shape and decision signals were weaker on occluded trials, supporting the hypothesis that they are derived via feedback from PFC. Overall these results provide insights into the interplay between visual and frontal cortex in the encoding of a dynamic stimulus and the discrimination of an occluded target.

Disclosures: E. Kempkes: None. **A. Bigelow:** None. **A. Pasupathy:** None.

Poster

PSTR083. Representation of Objects and Scenes

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Topic: D.06. Vision

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NEI grant R01 EY029601 to AP
Vision Core Grant P30EY01730 to UW Office of Research
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Title: Inserting Neuropixels probe into awake monkey cortex: two probes, three methods

Authors: *A. FYALL[1], E. KEMPKES[2], T. NAMIMA[3], A. PASUPATHY[4];
[1]Biol. Structure/Primate Ctr., [2]Biol. Structure, Univ. of Washington, Seattle, WA; [3]Osaka Univ., Suita, Japan; [4]Univ. Washington, Seattle, WA

Abstract: Inserting Neuropixels probe into awake monkey cortex: two probes, three methods
Amber Fyall*, Erin Kempkes*, Tomoyuki Namima*, Anitha Pasupathy
*Equal contribution
Neuropixels probes have revolutionized neurophysiological studies in the rodent, but inserting these probes through the much thicker primate dura remains a challenge. Here we describe three methods that we have developed for the insertion of two types of Neuropixels probes acutely into the awake monkey cortex. For the fine rodent probe (Neuropixels 1.0 aka. phase 3B2 , IMEC), which is unable to pierce native dura, we developed a method for insertion via a short, guide tube eyelet, based on a concept developed by Matsuzaka et al. (2009). We place a 3-4.5 mm long guide tube transdurally, anchored against the dural surface with an epoxy blob. This creates an eyelet for the insertion of the rodent probe. This method does not require a durotomy or probe sharpening and it is sufficiently versatile to work with any fragile, short probe. Downsides include potential damage to superficial cortex and the length of time that may be needed for probe insertion. The primate probe (Neuropixels NP1010, IMEC) is thicker and, when sharpened, can penetrate both a silicone artificial dura and the native dura immediately after a craniotomy. Given this, we have developed two additional methods for primate probe insertion. For probe insertions immediately after a craniotomy, we affix a custom-made silicone artificial dura on top of the native dura with Vetbond. This, combined with a sealed chamber system, retards tissue growth on the native dura and allows penetration with a sharpened probe for 6-8 weeks. For probe penetration within an older chamber with tougher dura, we have developed a system in which the native dura is replaced by an artificial dura. We have now conducted successful experiments in 4 animals across 8 recording chambers with the procedures described here and have achieved successful recordings over several months in each case. We will share details of hardware design, surgical preparation, methods for insertion and methods for removal of broken probe parts. We hope that our methods are of value to primate physiologists everywhere.

Disclosures: A. Fyall: None. **E. Kempkes:** None. **T. Namima:** None. **A. Pasupathy:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

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Program #/Poster #: PSTR083.27/X7

Topic: D.06. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health (ZIA EY000511)

Title: Short-latency preference for faces by visual neurons in the primate superior colliculus

Authors: *G. YU[1], L. N. KATZ[2], C. QUAIA[2], A. MESSINGER[2], R. J. KRAUZLIS[2];
[2]Natl. Eye Inst., [1]Natl. Eye Inst., Bethesda, MD

Abstract: Face processing is central to primates' survival. Neural mechanisms of foveal face processing have been extensively studied, leading to the discovery of face-selective regions in the temporal cortex (i.e., "face patches"). To engage these circuits, primates must first decide to foveate a potential face, a process about which much less is known. Here, we report that the superior colliculus (SC), a midbrain structure involved in visual selection and orienting, contains neurons that exhibit preferences for faces at short latencies. We recorded visually responsive neurons in the superficial and intermediate layers of the SC of two rhesus macaques while they passively viewed images presented in their receptive fields. We used 150 grayscale images of objects belonging to one of five categories previously used to test face processing in the temporal cortex: faces, bodies, hands, fruits/vegetables, and human-made objects. The 30 exemplar images in each category were matched in the distributions of low-level features (RMS contrast, size, and power in three spatial frequency bands). This allowed us to evaluate object selectivity in SC while controlling for low-level visual features. Many SC neurons exhibited a preference for faces within 50ms of stimulus onset, well before neurons in cortical face patches. Based on these short-latency responses, we trained a linear classifier to distinguish faces from other visual objects; the classifier achieved cross-validated accuracies of around 80%. To investigate the origin of this short-latency face preference, we inactivated the lateral geniculate nucleus, which relays visual signals from the retina to the visual cortex. This manipulation largely abolished visual responses in SC, including any face-related selectivity. We surmise that the short-latency face preference in SC depends on signals routed through the early visual cortex. Our results reveal an unexpected circuit in the primate visual system for rapidly detecting, and possibly orienting toward, face-like stimuli, complementing the higher-order visual areas needed for recognizing foveated faces.

Disclosures: G. Yu: None. **L.N. Katz:** None. **C. Quaia:** None. **A. Messinger:** None. **R.J. Krauzlis:** None.

Poster

PSTR083. Representation of Objects and Scenes

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.28/X8

Topic: D.06. Vision

Support: ZIA EY000511

Title: Effects of inactivating primate lateral geniculate nucleus on visual and movement-related activity in the superior colliculus

Authors: *L. N. KATZ[1], G. YU[2], R. J. KRAUZLIS[3];
[1]NIH, Bethesda, MD; [2]Natl. Eye Inst., [3]Richard Krauzlis, Natl. Eye Inst., Bethesda, MD

Abstract: In the primate, the primary target of retinal ganglion cells (RGCs) is the lateral geniculate nucleus (LGN), the main relay station from retina to cortex. A secondary target of primate RGCs is the superior colliculus (SC), a midbrain structure associated with visual processing and eye movements, that receives an estimated 10% of projections from the retina. These direct retinotectal projections have been speculated to support a range of visual functions, including express saccades, blindsight and possibly face detection, but their significance in visual processing is mostly unknown. Here, by comparing SC neuronal activity before and during LGN inactivation, we sought to identify which aspects of SC processing might be preserved when retinal inputs remained, but visual cortical inputs were temporarily blocked. We used linear arrays to record SC neurons in two rhesus monkeys and measured their visual and movement-related activity, before and during inactivation of the LGN. Visual responses were measured by presenting a variety of object stimuli in the neurons' receptive fields (RF) while the monkeys fixated. Movement related responses were measured during saccades directed into the neurons' RF, executed during intertrial intervals or during free viewing of nature videos. Inactivation of LGN was performed by injecting ~1µl of muscimol into its rostral pole and confirmed by documenting a visual scotoma—a region of the visual field in which monkeys could not detect stimuli —measured during a saccade task. An overlap between the scotoma and the SC neurons' RF was confirmed on all eight inactivation sessions. Only SC neurons with clear RFs were included in the analysis (182 overall). Before LGN inactivation, SC neurons exhibited strong visual responses to object stimuli in their RF. During LGN inactivation, visual responses were largely eliminated. This loss of responsiveness was evident across all SC neurons regardless of functional class: neither "visual neurons" (typically associated with the superficial layers of SC) nor "visual-movement" neurons (associated with the intermediate layers) responded to the onset of a stimulus in their RFs. Movement-related activity, in contrast, remained largely unchanged before versus during LGN inactivation, indicating that other non-visual inputs could still elicit activity.These results show that SC visual responses are mostly dependent on signals routed through the LGN and visual cortex, and that retinotectal inputs by themselves are insufficient to evoke SC responses. These results suggest that direct retinal projections to the SC may play no direct role in visual processing, at least in the adult macaque.

Disclosures: L.N. Katz: None. **G. Yu:** None. **R.J. Krauzlis:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.01/X9

Topic: D.07. Visual Sensory-Motor Processing

Support: Allen Institute AGR00023117

Title: Insights into the evolution of the animal nervous system from anatomical and functional studies in ctenophores

Authors: *C. BORBA, F. HUGOSSON, M. Q. MARTINDALE, J. STROTHER;
Whitney Lab. for Marine Biosci., Univ. of Florida, Saint Augustine, FL

Abstract: Recent analyses support ctenophores as the likely sister group to all other animals, making them a powerful model for understanding the origin and evolution of the animal nervous system. However, relatively little is known about the anatomy, functional architecture, and molecular biology of the ctenophore nervous system. Most ctenophore species have a structure called the apical sensory organ, which contains a gravity sensing statolith, ciliated cells that may be photosensitive, and papillae that may be pressure sensitive. Neurons from the apical sensory organ project to the comb rows, a structure of linked cilia used by the animal for locomotion. In this study, we examined the functional organization of the phototactic sensory-motor pathway in ctenophores using the cydippid stage of *Mnemiopsis leidyi* as a model. First, we used fluorescent *in situ* hybridization to label relevant gene markers, such as opsin and glutamate receptors. Next, calcium imaging was used to record the responses of neurons in the apical sensory organ to visual stimuli. The results from these experiments provide new details on the organization of this pathway and, by extension, fresh insights into the evolution of nervous systems in animals.

Disclosures: C. Borba: None. **F. Hugosson:** None. **M.Q. Martindale:** None. **J. Strother:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR084.02/X10

Topic: D.07. Visual Sensory-Motor Processing

Support: NSF DBI-2021795
NIH R01NS130917
NSF IOS-2212750

Title: Single Cell Atlas of Locust Optic Lobe Across Phases

Authors: *D. BELLINI, M. NIU, J. LUO, C. ZONG, F. GABBIANI;
Baylor Col. of Med., Houston, TX

Abstract: Single cell transcriptomics has become an increasingly popular tool to study a variety of biological problems, including identifying and annotating cell types. Characterizing the gene expression of various cell types has allowed to achieve a greater understanding of the inner workings of model organisms such as *Drosophila melanogaster*. *Schistocerca americana,* the American bird grasshopper, is a great model organism for neurophysiological experiments due to its brain size and large uniquely identifiable neurons, making it a favorable organism to conduct experiments involving neural recordings. However, the *Schistocerca americana* genome has only recently been published, and remains largely unannotated, while the *Drosophila melanogaster* genome has been extensively studied and profiled. To characterize the neurons present in the locust optic lobe, and to further understand visual processing in the locust brain, we created a single cell atlas of the *Schistocerca americana* optic lobe. To aid us in our annotation effort, we mapped the generated clusters to established *Drosophila* cell atlases. Our initial efforts indicate the presence of T4/T5 neurons homologs, which up until now were not known to exist in hemimetabolous insects. These neurons are directionally-selective motion detectors and have four subtypes, each one corresponding to one of the four cardinal motion directions (front-to-back, back-to-front, upwards and downwards). Additionally, we had strong mappings to other neuronal clusters, such as the photoreceptors. We also plan on producing dual single-cell optic lobe atlases of *Schistocerca gregaria*, the desert locust, in the gregarious and solitarious phases. Comparisons between the two atlases may reveal subtle gene expression changes in different cell types that could reveal the mechanisms of phenotypic plasticity changes at the single-cell level.

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.03/X11

Topic: D.07. Visual Sensory-Motor Processing

Support: HHMI

Title: What the fly eye tells the fly brain: visual projection neurons in the complete connectome of the Drosophila optic lobe

Authors: *P. SEENIVASAN, A. NERN, S.-Y. TAKEMURA, J. HOELLER, N. KLAPOETKE, E. GRUNTMAN, F. LOESCHE, K. LONGDEN, S. KOSKELA, E. ROGERS, A. ZHAO, M. DREHER, G. RUBIN, M. REISER;
Janelia Res. Campus, Ashburn, VA

Abstract: The nervous system of an adult, male fruit fly has been successfully imaged by Janelia's FlyEM team. The brain was prepared (fixed and embedded) for imaging using recently optimized protocols that preserve neuron morphology and enhance the contrast of membranes and synapses. The brain was cut into thick sections, followed by Focused Ion Beam milling and Scanning Electron Microscopy imaging (FIB-SEM). Subsequently, the entire volume was reassembled and Google Research's connectomics group carried out automatic segmentation of the volume into neuron fragments, which were then proofread by connectome annotators at Janelia. This has been a 3+ years process, with the right optic lobe being the first brain region to be proofread and analyzed. Together with a small group of collaborators, we have catalogued all neurons in the optic lobe, including the complete medulla (and accessory medulla), lobula, lobula plate, and approximately half of the lamina. Using first morphology analysis and then iterations of connectivity analysis, we identified and named all cell types of the optic lobe—over 51,000 neurons in ~700 cell types. The categorization of neurons already uncovered many interesting findings and many cell types were described for the first time. In ongoing analysis, we are examining regional variations, and using connectivity to predict both the spatial-visual properties of neurons, such as their putative receptive fields and their "participation" in various pathways. In this direction, we are currently analyzing the full set of Visual Projection Neurons (VPNs) that leave the optic lobe to target various central brain regions through direct or indirect pathways. Some of these central brain regions that are involved in vision-based learning are the posterior lateral and ventrolateral protocerebra (PLP and PVLP), mushroom body and the central complex. To provide context for functional experiments and understand the organization of visual pathways, we will present an input/output analysis of the VPNs. We sort the VPNs based on their inputs within the optic lobe to study whether they carry information about motion, ON or OFF signals, spatial-visual features, short versus long wavelengths, etc. Furthermore, by looking into whether the projection neurons target specific central brain areas or combinations of them, we provide detailed hypotheses about the nature of sensory information in the central brain.

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR084.04/X12

Topic: D.07. Visual Sensory-Motor Processing

Support: U19NS104653
1RO1NS124017
SCGB 542943SPI

Title: An interactive atlas platform for comparative anatomy in larval teleosts.

Authors: Y. ISOE[1], S. VOHRA[2], K. HERRERA[1], C. RIEGLER[1], H.-C. HEGE[2], D. BAUM[2], F. ENGERT[1];
[1]MCB, Harvard Univ., Cambridge, MA; [2]Zuse Inst. Berlin, Berlin, Germany

Abstract: Studying brain diversity and conserved neural circuits help us understand brain evolution. Comparative analysis between complementary model organisms accelerate deepening the study. We selected teleost larvae, medaka (*Oryzias latipes*) and zebrafish (*Danio rerio*) since they are transparent enough to visualize neurons and have small brains which facilitates whole brain analysis. Here, we establish a medaka larvae brain atlas (M-brain), expanded from existing zebrafish larval brain atlas (Z-brain) that allow us to map, explore and compare anatomical and functional substructures of two model species' brains. By using our new interactive platform, we compared volumes of the mutually exclusive and comprehensively exhaustive (MECE) regions in the whole brain across two species. Then we compared the miscellaneous (misc) region masks related to sensorimotor pathways and marker gene clusters, which are important properties in the research of system neuroscience. Finally, we show the comparison of the functional imaging to salt response and found medaka-specific responding regions.

Disclosures: Y. Isoe: None. **S. Vohra:** None. **K. Herrera:** None. **C. Riegler:** None. **H. Hege:** None. **D. Baum:** None. **F. Engert:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Topic: D.07. Visual Sensory-Motor Processing

Support: Azrieli Foundation
Israel Science Foundation 688/22
Binational Science Foundation 2021746
National Science Foundation 2207891

Title: Voltage imaging of distributed sensorimotor computations across the zebrafish brain

Authors: *S. ZADKA, I. SHAINER, T. KAWASHIMA;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Vertebrate sensorimotor behavior is mediated by a precise sequence of different neuronal activity types across the brain. Larval zebrafish is an ideal model for studying brain-wide neural dynamics, but technologies for recording neural activity at the millisecond time resolution have been limited. Here we performed population voltage imaging in three key areas for sensorimotor behaviors, including the optic tectum, cerebellum, and midbrain nucleus. The use of a light-sheet microscope with laser beam shaping and a new chemigenetic voltage indicator enabled to record from a large neuronal population stably for more than 10 minutes. We found diverse types of membrane potential modulation and spiking activity during the

optomotor response. Neurons in the midbrain nucleus showed fast activation that precedes and encodes motor outputs, whereas neurons in the cerebellum and optic tectum showed delayed activation that may represent efference copy. These results provide a glimpse into the flow of sensorimotor computations in the millisecond time resolution across brain areas and demonstrate the potential for further scaling up this methodology to the whole-brain scale.

Disclosures: S. Zadka: None. **I. Shainer:** None. **T. Kawashima:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR084.06/X14

Topic: D.07. Visual Sensory-Motor Processing

Support: ARC DECRA DE220100691

Title: Fear-dependent changes in perception and sensory representation in larvae zebrafish

Authors: *C. C. Y. LEE, E. K. SCOTT;
Anat. and Physiol., Univ. of Melbourne, Melbourne, Australia

Abstract: An animal's behavioral state is reflected in the dynamics of population activity and its capacity to process sensory information. Previous studies in mammalian brains have demonstrated a relationship between behavioral states and information processing. However, these studies have been limited to exploring how population dynamics and sensory representation changes in specific cortical areas. Thanks to its transparency at early life stage and the advent of selective plane illumination microscopy, the zebrafish brain is an attractive model that allow for whole brain imaging at single-cellular resolution. Here, we developed 4 behavioral paradigms using high-speed videography and tracking with deep neural network, to assess how sensory representation is altered under a state of fear. N=602, 6dpf zebrafish (*danio rerio*) were exposed to either a dark visual flash or varying volumes of loud noise burst. These target stimuli were preceded by either a visual loom or an auditory crescendo, mimicking an approaching threat. Fish showed both startle and freezing behavior following a loom or crescendo and altered their startle response to the target stimuli. Interestingly, the probability of startle and freeze response was dependent on the intensity of the target stimulus following a threat stimulus. The observed changes in behavioral output suggest a possible change in sensory representation and decision-making. How these changes arise in specific brain areas and across the entire brain remains to unknown, but the parameters established here represents a fruitful starting point to integrate with selective plane illumination microscopy for further investigations.

Disclosures: C.C.Y. Lee: None. **E.K. Scott:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR084.07/X15

Topic: D.07. Visual Sensory-Motor Processing

Support: Edmond & Lily Safra Center for Brain Sciences (ELSC)

Title: Temporal synchrony and the neural underpinning of social behavior in zebrafish

Authors: *I. LIFSHITZ, Y. RUBINSTEIN, M. MOSHKOVITZ, S. TISHBY, L. AVITAN; Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: To survive and reproduce, animals significantly rely on the ability to maintain social interactions with conspecifics. These interactions are observed across various species, and the underlying neural circuits are largely conserved across all vertebrates. Nevertheless, little is known about the neural mechanism that integrate sensory information and transform it into social actions. To address this question, we recorded whole-brain neural activity from a focal head-fixed and tail-free larval zebrafish observing a freely swimming conspecific, along with high-speed behavioral recording of both fish. We predicted the intended movement of the focal fish using principal components analysis of its tail flicks. Movements of the focal fish showed a typical time lag of around 100 milliseconds after a movement of the conspecific. Importantly, for movements that obeyed this time lag, the focal fish was more likely to approach the conspecific, and its predicted turn angle was significantly correlated with the conspecific's position. In addition, neurons in the optic tectum of the focal fish showed responses to the social stimulus and were highly locked to all tail movements of the focal fish. These findings suggest that movements of others are integrated to allow the characteristic temporal synchrony of social behavior, and lay the foundations to study the underlying neural mechanisms of social vs. non-social actions.

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

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Topic: D.07. Visual Sensory-Motor Processing

Support: 2021ZD0204500

Title: A novel motoneuron to locus coeruleus pathway facilitates global neuronal modulation

Authors: *Q. DENG, L. CHEN, J. DU;
Inst. of Neuroscience, Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: Growing evidence from nematodes to mammal shows that ongoing behavior-related signals influence information processing in the brain. However, how the signal coordinates multiple brain regions remains to be identified. Using the larval zebrafishas an *in vivo* model, we found that the Locus Coeruleus (LC), which sends axon projections throughout the brain, receives extensive motor-feedback signals from motor neurons to facilitate global neuronal modulation with a manner of motor intensity-dependence. Electrophysiological recording shows that spontaneous LC firings tightly couple with motor activities. Activation of motor neurons in the spinal cord robustly induces LC firings. Furthermore, confocal imaging combined with *in vivo* recording shows that certain sub-class of interneurons in the spinal cord mediate the motor-to-LC signal. The motor-to-LC feedback signal contributes to decreasing regional coupling, which further enhances the flexibility of brain-wide neuronal sensory-motor processing, and thus improves the behavioral performance. These results suggest a previously unidentified synaptic input from the motor system to the LC system that mediates behavior state-dependent global neuronal modulation.

Disclosures: Q. Deng: None. **L. Chen:** None. **J. Du:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.09/X17

Topic: H.08. Learning and Memory

Support: Azrieli Foundation
Israel Science Foundation 688/22
Binational Science Foundation 2021746
National Science Foundation 2207891
Israeli Council for Higher Education

Title: Motor learning by serotonergic disinhibition between serotonergic nuclei

Authors: *R. HARUVI, D. MALAMUD, I. SHAINER, T. KAWASHIMA;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: The serotonergic (5-HT) system in the vertebrate brain is involved in many aspects of brain functions and psychiatric disorders. It consists of several interconnected nuclei along the brainstem, and it was hypothesized to work as a mutually inhibitory network. This hypothesis has been challenging to address in mammalian brains due to the anatomical locus of the system.

Here, we found functional evidence for this hypothesis using whole-brain imaging of neural activity and serotonin release in zebrafish. We identified inhibitory interactions between serotonergic nuclei of different neural activity patterns during short-term motor learning behavior. Disinhibition of the dorsal raphe nucleus from such interaction was critical for the expression of the motor learning effect. Such inhibitory motifs in the serotonergic circuit may have broad implications for how the serotonergic system expresses its diverse functionalities depending on behavioral contexts.

Disclosures: **R. Haruvi:** None. **D. Malamud:** None. **I. Shainer:** None. **T. Kawashima:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.10/Web Only

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant 1U19NS104653-01
NIH Grant 5U19NS104653-04

Title: Dissection of a neuronal integrator circuit through correlated light and electron microscopy in the larval zebrafish - Part 1: Functional imaging and ultrastructure in the same animal.

Authors: *J. BOULANGER-WEILL[1,2], G. F. SCHUHKNECHT[1], F. KÄMPF[3], H. NAUMANN[3], M. PETKOVA[1], M. JANUSZEWSKI[4], M. STINGL[1], A. HEBLING[1], R. SCHALEK[1], G. FLEISHMAN[5], F. DEL BENE[2], J. W. LICHTMAN[1], F. ENGERT[1], A. BAHL[3]; [1]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [2]Inst. de la Vision, Paris, France; [3]Dept. of Biol., Univ. of Konstanz, Konstanz, Germany; [4]Google Res., Zürich, Switzerland; [5]Janelia Farm, Ashburn, VA

Abstract: Specific synaptic connectivity between neurons forms the scaffold of neuronal computations essential for cognition and behavior. Experimental approaches combining neuronal recordings and synaptic connectivity reconstruction in the same animal can resolve their structural implementation. Here, we apply this approach to test possible circuit arrangements in the larval zebrafish hindbrain that performs evidence accumulation in a noisy motion integration task.
First, using calcium imaging, machine-learning-based cell segmentation methods and single trial regressors analysis we identified ~500 hindbrain neurons involved in the task. As previously described these neurons were sensory integrators, dynamic threshold and motor command neurons. This fish was then imaged using electron microscopy and automated single cell alignment was used to superimpose light microscopy (activity and cell type labeling data). We used a novel segmentation-free approach which greatly improved previous manual registration both in terms of time requirement and precision.

Second, this multimodal dataset was uploaded into a Neuroglancer 3D browser which allows data visualization and collaborative tracing to test connectivity hypotheses. Preliminary EM reconstructions of 30 identified integrator neurons indicate that the majority of these neurons (20/30) sent inhibitory drive to the contralateral side which supports the hypothesis of inter-hemispheric mutual inhibition. Remaining integrator neurons sent an excitatory drive to the ipsilateral side. These excitatory neurons sent and received multiple mono-synaptic inputs to/from other ipsilateral integrator neurons supporting the recurrent connectivity hypothesis. We also reconstructed 8 dynamic threshold neurons controlling motor gating. The majority of these neurons projected to the contralateral side. This rejects our proposed circuit model in which dynamic threshold cells remained exclusively within one hemisphere. However, our preliminary analysis of the neurotransmitter identity of these cells suggests that they are all inhibitory, as we previously suggested. Current work aims at describing the implementation of motor command gating.
In summary, we demonstrate how correlated light and electron microscopy enables synaptic-resolution circuit analyses in the zebrafish nervous system and mechanistic understanding of vertebrate neuronal computation from sensory to motor systems. Using these tools and datasets we hope to help the zebrafish community to perform structure function analyses of brain circuits.

Disclosures: **J. Boulanger-Weill:** None. **G.F. Schuhknecht:** None. **F. Kämpf:** None. **H. Naumann:** None. **M. Petkova:** None. **M. Januszewski:** None. **M. Stingl:** None. **A. Hebling:** None. **R. Schalek:** None. **G. Fleishman:** None. **F. Del Bene:** None. **J.W. Lichtman:** None. **F. Engert:** None. **A. Bahl:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.11/X18

Topic: D.07. Visual Sensory-Motor Processing

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NIH Grant 5U19NS104653-04
Simons Foundation SCGB 542943SPI
Swiss National Science Foundation Grant P2EZP3_188017
Swiss National Science Foundation Grant P500PB_203130

Title: Dissection of a neuronal integrator circuit through correlated light and electron microscopy in the larval zebrafish - Part 2: Ultrastructural analysis of the anterior hindbrain.

Authors: J. BOULANGER-WEILL[1,2], ***G. F. P. SCHUHKNECHT**[1], F. KÄMPF[3], H. NAUMANN[3], M. PETKOVA[1], M. JANUSZEWSKI[4], M. STINGL[1], A. HEBLING[1], R. SCHALEK[1], G. FLEISHMAN[5], F. DEL BENE[2], J. W. LICHTMAN[1], F. ENGERT[1], A. BAHL[3]; [1]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [2]Inst. de la Vision, Paris, France;

[3]Dept. of Biol., Univ. of Konstanz, Konstanz, Germany; [4]Google Res., Zurich, Switzerland; [5]Janelia Farm, Ashburn, VA

Abstract: When larval zebrafish experience whole-field visual motion, as in the random-dot task, they swim in the direction of motion, an innate behavior enabling animals to maintain position in moving water. Intriguingly, this behavior is well explained by the same bounded drift-diffusion model that captures human and primate behavior in analogous random-dot paradigms. We previously proposed a functional circuit model that implements this algorithm via a neural integrator circuit in the anterior hindbrain that accumulates noisy visual evidence and excites downstream motor circuits after overcoming competitive inhibition from surrounding neurons. This study is part of a multipronged collaborative effort to correlate functional responses of hindbrain neurons with their ultrastructure and synaptic connectivity with the goal to systematically test and revise our proposed circuit model. Here, we employ a sparse connectomics approach to systematically map the anatomical cell classes and their connectivity in the anterior hindbrain to test if the proposed anatomical motifs are indeed present. We analyzed data from an unpublished electron microscopy volume acquired from a seven-day old zebrafish larva, containing 170,000 neurons and glia cells from the central and peripheral nervous system. First, we used AI-assisted cell reconstructions in Neuroglancer of 25 randomly selected neurons in the anterior hindbrain. A complementary approach of two-photon guided photoactivation of neurons whose responses were functionally identified showed that integrator neurons cluster into two anatomical classes: an ipsilateral projection class (Class 1) and a contralateral projection class (Class 2). 23 out of our 25 reconstructed neurons matched this classification. We traced the postsynaptic partners of six Class 1 cells (n = 196) and one Class 2 cell (n = 116). Intriguingly, Class 1 neurons separated further into two ‘output types’: Type 1 contacted other Class 1 and 2 cells and neurons projecting to the motor nuclei of the reticulospinal system; this putatively provides the anatomical substrate for a recurrent integrator. Type 2 predominantly targeted neurons in the raphe and formed few synapses with other cells. By contrast, the Class 2 cell synapsed on all of these identified postsynaptic cell types in the contralateral hemisphere, which could mediate the interhemispheric inhibition that was proposed to determine swim direction. In the next step, we will specifically map the synaptic circuitry between Class 1 neurons. Combining this with our targeted photoactivations could provide a detailed structure-function mapping of the recurrent integrator motif.

Disclosures: **J. Boulanger-Weill:** None. **G.F.P. Schuhknecht:** None. **F. Kämpf:** None. **H. Naumann:** None. **M. Petkova:** None. **M. Januszewski:** None. **M. Stingl:** None. **A. Hebling:** None. **R. Schalek:** None. **G. Fleishman:** None. **F. Del Bene:** None. **J.W. Lichtman:** None. **F. Engert:** None. **A. Bahl:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.12/X19

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH U19
Emmy Noether (DFG)
Zukunftskolleg (University of Konstanz)
Centre for the Advanced Studies of Collective Behavior (University of Konstanz)

Title: Dissection of a neuronal integrator circuit through correlated light and electron microscopy in the larval zebrafish - Part 3: Functional imaging, anatomy, and neurotransmitters.

Authors: J. BOULANGER-WEILL[1], G. F. SCHUHKNECHT[1], **F. F. KÄMPF**[2], H. NAUMANN[2], M. PETKOVA[1], M. JANUSZEWSKI[3], A. HEBLING[1], M. R. STINGL[1], R. SCHALEK[1], G. FLEISHMAN[4], F. DEL BENE[5], J. W. LICHTMAN[1], F. ENGERT[1], *A. BAHL[2];
[1]Harvard Univ., Cambridge, MA; [2]Univ. of Konstanz, Konstanz, Germany; [3]Google Res., Zürich, Switzerland; [4]Janelia Res. Campus, Ashburn, VA; [5]Inst. de la Vision, Paris, France

Abstract: It is poorly understood how neural networks integrate information and guide sensory-motor decision-making. We have recently identified an area in the larval zebrafish anterior hindbrain that temporally integrates sensory information during a random-dot-motion visual discrimination task. Based on calcium imaging experiments, we proposed a potential anatomical circuit arrangement that we are now dissecting here in detail. We employ a series of three complementary approaches. We first develop a novel cell-specific mapping approach to correlate light microscopy and electron microscopy (CLEM) in the same animal (Part 1: Functional imaging and ultrastructure in the same animal). Using a second electron microscopic volume of another fish, we then build a comprehensive library of anatomical reconstructions at synaptic resolution across the entire brain (Part 2: Ultrastructural analysis of the anterior hindbrain). In this poster (Part 3: Functional imaging, anatomy, and neurotransmitters), we employ two-photon guided GFP photoactivations and HCR FISH-based neurotransmitter identification methods to link neural dynamics to circuit structure in the same animal. Together, these three approaches provide a powerful toolkit for detailed dissections of neural circuit function, from sensory perception, to temporal integration, to behavioral decision-making.

Disclosures: J. Boulanger-Weill: None. **G.F. Schuhknecht:** None. **F.F. Kämpf:** None. **H. Naumann:** None. **M. Petkova:** None. **M. Januszewski:** None. **A. Hebling:** None. **M.R. Stingl:** None. **R. Schalek:** None. **G. Fleishman:** None. **F. Del Bene:** None. **J.W. Lichtman:** None. **F. Engert:** None. **A. Bahl:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.13/X20

Topic: D.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute
Simons Foundation 542943SPI

Title: Brain states modulate neural computation across most of the zebrafish brain

Authors: *J. LIM[1,2], **Z. WEI**[1], S. NARAYAN[3], X. MI[4], W. ZHENG[4], D. E. BERGLES[2], G. YU[4], M. RUBINOV[5], J. FITZGERALD[1], M. B. AHRENS[1];
[1]Janelia Res. Campus, Ashburn, VA; [2]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Allen Inst., Seattle, WA; [4]Virginia Tech., Blacksburg, VA; [5]Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: Animals can change brain and behavioral states based on past experience. How such states affect brain-wide neural computations remains unknown. Here we elicit covert brain states (i.e. states that persist even in the absence of behavior) that result from animals experiencing control or lack of control, leading to states that are normal or in which they remain behaviorally quiescent for a period (passive), using closed- or open-loop virtual reality (VR) environments. Subsequent to state changes, moving the animal backward in pulses in VR, we examined and compared the animal's capability for sensorimotor transforms in normal versus passive states. In normal states, an animal can track and integrate the visual flow over time and then generate a behavioral response (like a drift-diffusion process). This process was slowed in a passive state. Using calcium imaging, we monitored whole-brain dynamics while animals were behaving in VR. We find a plethora of brain-wide changes covering ~40% of all brain neurons and modulation of computation at all stages of the sensorimotor transformation. Brainwide neural dynamics were overall dampened in the passive state, yet a few motor-related brain regions increased their activity in the passive states (e.g. preoptic area, IPN, L-MO). A subset of visual responses was altered. Accumulating motion responses, integrative motor preparation responses, and pulsatile premotor responses were also all dampened in the passive state, spanning the IO, cerebellum, SLO-MO, mid- and forebrain regions and more. A brain-wide population of premotor neurons show sensory integration that is slowed down after giving up. These changes collaborate to slow down the behavioral response to the body displacements. Large-scale release of norepinephrine and activation of brain-wide astroglia populations are present during state changes and may underlie these functional changes. These results show that state-dependent behavior emerges from orchestrated modulation of a large fraction of surprisingly functionally diverse brain circuits.

Disclosures: **J. Lim:** A. Employment/Salary (full or part-time):; Johns Hopkins University (USA), Agency for Science, Technology and Research (Singapore). 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.; Howard Hughes Medical Institute. **Z. Wei:** A. Employment/Salary (full or part-time):; Howard Hughes Medical Institute. 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.; Simons Foundation 542943SPI. **S. Narayan:** A. Employment/Salary (full or part-time):; Allen Institute. **X. Mi:** A. Employment/Salary (full or part-time):; Virginia Tech. **W. Zheng:** A. Employment/Salary (full or part-time):; Virginia Tech. **D.E. Bergles:** A. Employment/Salary (full or part-time):; Johns Hopkins University. **G. Yu:** A. Employment/Salary (full or part-time):; Virginia Tech. **M. Rubinov:** A. Employment/Salary

(full or part-time):; Vanderbilt University. **J. Fitzgerald:** A. Employment/Salary (full or part-time):; Howard Hughes Medical Institute. **M.B. Ahrens:** A. Employment/Salary (full or part-time):; Howard Hughes Medical Institute.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.14/X21

Topic: D.07. Visual Sensory-Motor Processing

Title: Neural circuits underlying optomotor responses in larval teleost fish

Authors: *K. E. FOUKE, S. M. GORBATOV, M. D. LORING, E. A. NAUMANN; Neurobio., Duke Univ., Durham, NC

Abstract: While many sensory cues appear continuously, animals often respond by moving discretely, with a defined start and end. For instance, to compensate for retinal slip, the brain converts continuous visual motion cues into motor outputs with specific speed and duration. Due to its experimental advantages, the larval zebrafish allows detailed investigations of these universal neural computations in vertebrates. Specifically, during the optomotor response (OMR), the larval zebrafish moves in short burst-and-glide swims (i.e., bouts) to stabilize its position in continuous optic flow. Yet, while the closely related translucent fish species *Danionella cerebrum* inhabits natural environments comparable to zebrafish, larval *Danionella* fail to burst-and-glide, preferring instead to move in continuous swims. These natural differences in behavior provide a unique opportunity to investigate and compare the neural encoding of this sensorimotor transformation. Here, we characterize larval *Danionella* OMR behaviors by presenting direction and eye-specific motion patterns in freely-swimming, closed loop tracking assays. We compare OMR kinematic metrics, including gain, velocity, and locomotion duration, between larval *Danionella* and zebrafish (n > 10 fish). Results show that *Danionella* follow direction of motion comparable to zebrafish but continuously swim at a slower speed. To correlate these visually evoked behaviors with neural activity, we use head-fixed volumetric two-photon calcium imaging and simultaneous high-speed tail tracking. We find that both fish species contain a multitude of diverse motion responsive neurons in homologous visual processing brain regions. The retinorecipient pretectum and downstream hindbrain regions, for example, display lateralized motion encoding and species-specific neural correlates of behavior. This study provides a framework to identify the mechanisms underlying discrete and continuous locomotion in vertebrate sensorimotor transformations.

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.15/X22

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant RF1NS128895

Title: Functional and molecular characterization of motion-processing neurons in the larval zebrafish

Authors: *W. S. JACOBS, M. D. LORING, J. CHOO-CHOY, R. PULUGURTA, M. NIKITCHENKO, T. W. DUNN, E. A. NAUMANN;
Neurobio., Duke, Durham, NC

Abstract: The transformation of visual input into behavior requires complex circuits of diverse neurons, yet there exists a gap in understanding how these neurons are connected and influence neural response dynamics. Recent studies into the visually guided optomotor response (OMR) in larval zebrafish have attempted to bridge this gap by proposing circuit models that predict connectivity among common functionally identified response classes of motion-processing neurons. However, these models ignore the diversity of these neurons, lack their molecular profile, and fail to capture inherent circuit dynamics. Here, we performed two-photon calcium imaging while presenting moving gratings as visual stimuli to 6-8 dpf larval zebrafish (n=10) expressing GCaMP6s. By co-expressing fluorescent red markers to identify excitatory or inhibitory neurons with vglut2a or gad1b promoters, we found glutamatergic and GABAergic neurons within all major response classes. With hierarchical clustering, we discovered that classes with a higher percentage of glutamatergic neurons tend to respond to fewer stimuli and are more suppressed when presented with motion in the direction opposite of their tuning. In contrast, classes with a higher percentage of GABAergic neurons tend to respond to more stimuli and are less suppressed. To generate hypotheses about functional connectivity, we trained recurrent neural networks (RNNs) with calcium imaging data to model the connections within the pretectum and their influence on hindbrain motor areas. We constrained our models with known anatomical connections, with model neurons receiving input from the contralateral retina and connecting to the ipsilateral and contralateral pretectum. Our model predicts strong excitatory connections are more common among neurons with similar visual tuning, whereas inhibitory connections are more common among neurons with opposite tuning. With current based decomposition (CURBD), we determined that model neurons rise in circuit influence during presentation of motion in their tuned direction. By decomposing the solution matrix and examining its eigenvalues, we found consistency in our model across hundreds of training runs. In summary, we provide a detailed classification of OMR motion-processing neurons that considers their neurotransmitter identity and diverse dynamics in addition to their stimulus selectivity and employ an RNN model to generate predictions of functional connectivity relevant for OMR visual processing. Together, these findings advance the field closer to a mechanistic understanding of how visual motion signals are transformed by diverse neurons into perception and behavior.

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.16/X23

Topic: D.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute
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Azrieli Foundation
Israel Science Foundation 688/22
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National Science Foundation 2207891

Title: Multimodal voltage and neurotransmitter imaging of input-output dynamics reveals sensorimotor learning in the serotonergic system

Authors: *Z. WEI[1], T. KAWASHIMA[2], R. HARUVI[3], L. M. PANINSKI[4], M. B. AHRENS[1]; [1]Janelia Res. Campus, HHMI, Ashburn, VA; [3]Weizmann Inst. of Sci., [2]Weizmann Inst. of Sci., Rehovot, Israel; [4]Columbia Univ., New York, NY

Abstract: Animals dynamically adjust their body movements by observing the sensory outcomes of motor commands. In larval zebrafish, serotonergic neurons in the dorsal raphe nucleus mediate such motor learning by responding to the motion of external sensory cues during swimming. Yet it remains elusive how it integrates sensorimotor information at a cellular level during such learning. By using voltage imaging, glutamate and GABA imaging and serotonin imaging, we found that serotonergic neurons receive precise temporal sequences of motor-driven inhibition and sensory-driven excitation during each swim event. Rebound depolarization from inhibition and sensory-driven excitation synergistically induced spiking of serotonergic neurons, resulting in rhythmic serotonin release to the downstream circuits between swim events. Ablation of dorsal raphe GABAergic neurons decreased inhibition on serotonergic neurons and impaired sensory cue responses, suggesting that motor-driven inhibition triggers sensorimotor learning via serotonergic neurons. Our findings demonstrate the precise computational ability of the serotonergic system which may underlie its roles in broader behavioral contexts.

Disclosures: **Z. Wei:** None. **T. Kawashima:** None. **R. Haruvi:** None. **L.M. Paninski:** None. **M.B. Ahrens:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.17/X24

Topic: D.07. Visual Sensory-Motor Processing

Support: NSERC Discovery Grant RGPIN-2021-02977

Title: Pretectal optic flow processing in zebra finches during flight

Authors: *E. R. PRESS[1], V. B. BALIGA[1], S. DASH[1], D. R. WYLIE[2], D. L. ALTSHULER[1]; [1]Zoology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Many animals including birds and humans depend on global visual motion, commonly termed *optic flow*, to guide movement through natural environments[1].
In all tetrapods, the pretectal nucleus *lentiformis mesencephali* (LM) contains retina-recipient neurons that respond to optic flow stimuli, and demonstrate tuning with respect to direction, speed, and in the spatiotemporal domain[2,3.] LM is homologous to the mammalian pretectal nucleus of the optic tract. Neural inactivation experiments[4] and electrophysiology paired with eye tracking[5,6] have demonstrated that LM is implicated in image stabilizing optokinetic responses. Given the physiology and connectivity of LM, it is expected to also play a role in the analysis of optic flow during locomotion.
However, LM function has never been investigated during natural locomotion. Given the importance of optic flow to flight control, our foundational hypothesis is that LM neurons are modulated by optic flow during flight. We therefore developed *in vivo* electrophysiology to record spiking activity of LM neurons in freely flying zebra finches. The system produces stable single-unit recordings for over 3 months of free behaviour and head-fixed psychophysical experiments. Analyses focus on the responses of LM neurons to flight-induced optic flow, head turn-induced optic flow, and exogenous optic flow cues presented along the lateral walls of the flight chamber. We have found that LM neurons display consistent tuning to optic flow stimuli under anesthesia and in awake, head-fixed conditions. Most LM neurons preferred forward motion and were suppressed by flight-induced backward motion. However, some neurons could be excited by exogenous forward motion during flight, suggesting a portion of LM neurons faithfully report sensory driven optic flow during flight. We also discovered neurons that display weak directional tuning but are highly modulated during flight. These findings suggest that LM contains neuronal sub-types that may not be fully captured by anesthetized recordings. LM likely participates in visuomotor transformations during locomotion, extending its role beyond optokinetic responses. Literature cited:1 Gibson JJ (1950). The perception of the visual world. *Boston: Houghton Mifflin*2 Winterson BJ, and Brauth SE (1985) *Exp Brain Res*3 Wylie RW, and Crowder NA (2000) *J. Neurophys*4 Gioanni H, *et al (*1983) *Exp Brain Res*5 Gioanni H, *et* al (1984) *Exp Brain Res*6 Yang *et al* (2008) *Nat Neurosci*

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Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.18/X25

Topic: D.07. Visual Sensory-Motor Processing

Title: Inferior Colliculus(IC) recordings in a mice hunting hidden crickets

Authors: *N. SHETTIGAR, J. TERAN, J. VOIGTS, E. DENNIS;
Janelia Res. Campus, Ashburn, VA

Abstract: Drawing inspiration from nature, we developed a naturalistic behavior paradigm of mice hunting for crickets, guided by sensory cues, in a large arena. This hexagonal arena (2 meters wide), is comprised of modular hexagon tiles, creating a repeated Y maze structure. The individual tiles have walls and as the animal navigates through the arena, whenever the animal stops moving (pauses), a speaker in one of the tiles plays cricket chirp noises. If they enter the correct tile location producing chirps, a trap door opens and a cricket becomes available. The task begins with the mice exploring the space without any auditory stimulus. Next, cricket chirps come from a new location where an animal can receive a cricket. This process continues for the duration of the experimental session. As an auditory driven task, we decided to probe inferior colliculus(IC) as the mice explores and navigates this space finding crickets. Previous studies have shown that the IC receives and integrates different modalities of inputs including auditory, somatosensory, visual, and motor. We implanted a window to record neural activity in IC, and report activity dynamics and correlate with task variables as this freely moving animal finds hidden crickets.

Disclosures: **N. Shettigar:** None. **J. Teran:** None. **J. Voigts:** None. **E. Dennis:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

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Program #/Poster #: PSTR084.19/Y1

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Title: Cortico-tectal circuits involved in motor preparation and navigation

Authors: *T. LUPASHINA[1,2], R. BERGMANN[3], K. SEHARA[3], S. DOMINIAK[3], J. SIBILLE[1,2], K. TEH[1,2], I. KHALID[1,2], M. E. LARKUM[3], R. N. SACHDEV[3], J. KREMKOW[1,2]; [1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Bernstein Ctr. for Computat. Neurosci., Berlin, Germany; [3]Inst. of Biology, Humboldt-Universität, Berlin, Germany

Abstract: Cortico-collicular interactions are thought to mediate a range of multimodal sensorimotor behaviors, including navigation, orientation, and decision making. Layer 5 pyramidal neurons distributed in widespread cortical areas connect cortex to superior colliculus (SC) and collicular output targets higher order thalamic nuclei. The thalamo-cortical neurons then generate feedback in the cortex. How and when these multiregional circuits interact during complex sensorimotor behavior is still largely unknown. When head-fixed mice navigate a plus-maze on an Airtrack system (Nashaat et al. 2016), they orient their body to the maze and they coordinate the movement of their torso and limbs with the movement of their whiskers and eyes (Bergmann et al, 2021). The whiskers and eyes move in a look-ahead fashion and independently predict the turn direction that mice impose on the maze. Here we begin to test the hypothesis that the cortico-collicular-thalamic circuits are causal in the planning and execution of these sensorimotor behaviors. Our first aim was to causally test the contribution of the different circuits on the behavior, by inactivating the circuits by optogenetic activation of inhibitory neurons in VGAT-ChR2 mice. Our preliminary data shows that driving VGAT neurons in SC robustly evokes contraversive ocular, whisker, and facial movements; supporting the hypothesis that SC is involved in the task. We then studied how the neuronal activity in superior colliculus and motor cortical areas (secondary motor cortex (M2), MOs) is related to these behaviors. We targeted and recorded neuronal activity from across SC layers and in M2 with the use of Neuropixels probes which can record simultaneously from a large population of neurons (Sibille et al, 2022). In the preliminary analysis of these recordings, we observed distinct and diverse neuronal activity in both M2 and SC linked to the movement of the mouse on the airtrack platform. With further optogenetics and extracellular recordings, we hope to extend our understanding of the cortico-collicular role in specific movements needed for multimodal orienting and navigating behaviors.

Disclosures: T. Lupashina: None. **R. Bergmann:** None. **K. Sehara:** None. **S. Dominiak:** None. **J. Sibille:** None. **K. Teh:** None. **I. Khalid:** None. **M.E. Larkum:** None. **R.N. Sachdev:** None. **J. Kremkow:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.20/Y2

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant EY022951

Title: Flexible perceptual encoding by discrete gamma events

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Abstract: Cognitive processes underlying behavior such as navigation, attention, and perception are linked to specific spatiotemporal patterns of neural activity in the neocortex. These patterns arise from synchronous synaptic activity and are often detected in particular frequency bands in the cortical field potential. However, cortical activity is highly variable on multiple timescales (milliseconds to hundreds of seconds). Identifying discrete neural events underlying patterned activity within highly dynamic cortical network fluctuations thus remains a critical challenge. Here, we develop a novel analytical method to track individual network events underlying state-dependent activity with single-cycle precision. In mouse primary visual cortex (V1), we find that events underlying activity in the γ- (30-80Hz) range are selectively associated with enhanced visual encoding by V1 neurons. γ events are linked to a propagation of activity from cortical layers 4 to 2-3 and 5 strongly suggesting thalamocortical integration of visual information coming from the retina. Accordingly, the spectral and laminar profile of γ activity can be recreated by patterned optogenetic stimulation of thalamocortical terminals. In behaving mice, γ event rate increases steadily prior to visually-cued behavioral responses, predicting trial-by-trial visual detection performance. This relationship between γ events and behavior is sensory modality-specific and rapidly modulated by changes in task objectives, but unaffected by behavioral state. γ events thus support a selective and flexible encoding of visual information according to behavioral context, suggesting a major role for these transient patterns of cortical activity.

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Poster

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Title: Investigating brain-wide encoding through interpretable subspaces

Authors: *Y. LIU[1], S. CHEN[3], Z. WANG[2], B. KANG[1], N. LI[4], K. SVOBODA[5], S. DRUCKMANN[1];
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Abstract: Behavior related activity in decision making tasks is encoded across multiple brain areas, suggesting a multi-regional basis for its computation. However, how encodings from multiple brain areas differ and coordinate remains an open question. We analyzed brain-wide encoding while mice performed a delayed-response movement task. The data consisted of dozens of sessions with simultaneously recorded activity of hundreds of neurons across multiple brain areas, using up to 5 Neuropixel probes. The recording targeted the anterior lateral motor cortex (ALM) and its connected areas (the medulla, midbrain, striatum, and thalamus). We first analyzed the encoding of behavior-related variables (sensory stimulus, behavioral choice) and compared encoding at the level of single trials across brain areas. The fraction of trials in which predictions from individual areas agreed was far higher than chance. We then evaluated the overlap of encoding between brain areas. Decoding analysis showed that during the movement planning, ALM contained more distinct choice information compared to other areas, while other areas contained more overlapping choice information. We then analyzed the relation between dynamics in area pairs using approaches that infer correlated activity, i.e., Canonical Correlation Analysis (CCA) and Reduced Rank Regression (RRR). Autoencoders were used to find a low-dimensional representation of movement from videography which was then used to link movement and activity. Together these analyses allowed us to explore three types of subspaces: those inferred by CCA and RRR, those used by behavioral decoders, and those related to movement captured by videos. We refer to these subspaces as the between-area-communication subspace (BACS), the coding subspace (CS), and the motor subspace (MS) respectively. Our analysis showed that although CS partially overlapped with MS, the majority of coding was independent of motor representations, suggesting a separation between decision making and movements related to decision. Finally, our analysis showed that BACS incorporates a much larger portion of MS than CS, suggesting CCA and RRR may be strongly influenced by common modes across brain areas caused by movement. In summary, we studied the brain-wide representations of coding, motor, and between-area communication by characterizing their respective interpretable subspaces and analyzing the relationships between them. Our work characterizes multi-regional encoding of short-term memory in mice and charts a path for study of different tasks and datasets.

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Poster

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Program #/Poster #: PSTR084.22/Y4

Topic: D.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute

Title: Facemap: a framework for modeling neural activity based on orofacial tracking

Authors: *A. SYEDA[1], L. ZHONG[1], R. TUNG[1], W. LONG[1], D. O'CONNOR[2], M. PACHITARIU[1], C. STRINGER[1];
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Abstract: Previous studies have shown that orofacial behaviors drive a large fraction of brainwide neural activity in mice. To understand the nature and function of these signals, we need better computational models to characterize the behaviors and relate them to neural activity. Here we developed Facemap, a framework consisting of a keypoint tracking algorithm and a deep neural network encoder for predicting neural activity. We used the Facemap keypoints as input for the deep neural network to predict the activity of~50,000 simultaneously-recorded neurons and in visual cortex we doubled the amount of explained variance compared to previous methods. Our keypoint tracking algorithm was more accurate than existing pose estimation tools, while the processing speed was several times faster, making it a powerful tool for closed-loop behavioral experiments. The Facemap tracker was easy to adapt to data from different experimental setups in other labs, requiring as few as 10 annotated frames for near-optimal performance. We showed that the neuronal activity clusters highly correlated with behavior were more spatially distributed across cortical regions. We also found that the deep keypoint features inferred by the model had time-asymmetrical state dynamics that were not apparent in the raw keypoint data. To expand the range of orofacial behaviors studied, we integrated a 2D tongue segmentation algorithm into Facemap, built from the small and fast Facemap network architecture. The tongue segmentation algorithm was just as accurate as previous segmentation methods, while achieving inference speeds that were several times faster than previous methods. The tongue segmentations can be subsequently used to extract various tongue kinematics and study their relation to neural activity. In summary, Facemap provides a stepping stone towards understanding the function of the brainwide neural signals and their relation to mouse orofacial behaviors.

Disclosures: **A. Syeda:** None. **L. Zhong:** None. **R. Tung:** None. **W. Long:** None. **D. O'Connor:** None. **M. Pachitariu:** None. **C. Stringer:** None.

Poster

PSTR084. Sensorimotor Transformations: Circuit Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR084.23/Y5

Topic: D.07. Visual Sensory-Motor Processing

Support: 5U19NS123716-02

Title: Engaged decision-makers synchronize their spontaneous movements to stereotyped task events

Authors: *C. YIN[1], M. MELIN[1], G. ROJAS-BOWE[1], S. GLUF[2], X. R. SUN[3], A. KOSTIUK[1], S. MUSALL[4], A. CHURCHLAND[1];
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Abstract: Neural activity during sensory-guided decision-making tasks is strongly modulated by the animal's movements. Although the impact of movements on neural activity is now well-documented in multiple species, the relationship between these movements and behavioral performance remains unclear. To understand this relationship, we first tested whether the magnitude of animal movements (assessed by the motion energy of 28 DeepLabCut-labeled body parts) was correlated with its performance on a perceptual decision-making task. No strong relationship was present, suggesting that task performance is not affected by the magnitude of movements. We then tested if performance instead depends on movement timing and trajectory. We therefore partitioned the movements into two groups: task-aligned movements that were well predicted by task events (such as the onset of the sensory stimulus or the animal's choice) and task independent movements (TIM) that occurred independently of task events. TIM had a reliable, inverse correlation with performance in 8/9 head-fixed mice and 4/4 freely moving rats. This argues that certain movements, defined by their timing and trajectories relative to task events, might indicate periods of engagement or disengagement in the task. To confirm this, we compared TIM to the latent behavioral states recovered by a hidden Markov model with Bernoulli generalized linear model observations (GLM-HMM) and found these, again, to be inversely correlated. Finally, we examined the impact of these behavioral states on neural activity measured with wide field calcium imaging. Our linear encoding model could account for more overall variance in neural activity in the disengaged state, likely because of the preponderance of TIM during that time. Interestingly, the engaged state was associated with widespread increased activity, particularly during the delay period. Taken together, these findings suggest that TIM is informative about an animal's internal state of engagement, and that the movements and state together have a major impact on neural activity, especially during the most cognitively demanding moments in a decision.

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Poster

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Program #/Poster #: PSTR084.24/Y6

Topic: D.07. Visual Sensory-Motor Processing

Support: Howard Hughes Medical Institute

Title: Disentangling sensory, motor and cognitive variables with Rastermap

Authors: *C. STRINGER, L. ZHONG, A. SYEDA, F. DU, M. PACHITARIU;
HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Large-scale neural activity contains high-dimensional representations of sensory, motor and cognitive variables. These variables cannot be easily disentangled by existing data visualization methods. We therefore developed an embedding algorithm called Rastermap, which captures complex temporal and highly nonlinear relationships between neurons, and provides useful visualizations by assigning each neuron to a location in the embedding space. Rastermap discovered structure in a variety of datasets: spontaneous neural activity, neural activity during a virtual reality task, widefield neural imaging data from a 2AFC task, fish whole-brain neural activity, rat hippocampal electrophysiological data, responses of real and artificial neurons to thousands of visual stimuli, and artificial neural activity from an agent playing atari games. For example, in spontaneous neural activity, we recovered populations of neurons related to interpretable orofacial behaviors. In neural activity recorded while the mouse performed a virtual reality task, we discovered sequences of neurons activated in visual areas, distinct from neural activity driven by motor variables. Further, we found a separation of unsupervised and supervised learning signals across visual areas. A graphical user interface is provided with Rastermap to easily run the algorithm without writing code and also to explore spatial relationships across neurons in the visualization. We look forward to the application of Rastermap across various neural recording modalities to uncover the building blocks of neural computations.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR085.01/Y7

Topic: E.02. Cerebellum

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MOST 107-2321-B-002-020

MOST 108-2321-B-002-011
MOST 108-2321-002-059-MY2
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MOST 111-2628-B-002-036
NTUMC 110C101-011
NSC-145-11
NTUH 108-039
NIH R01NS118179
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Title: The cerebellum constructs motor kinematics and tremor by quantitatively encoding instantaneous motor frequencies.

Authors: Y.-M. WANG[1], C.-W. LIU[2], S.-Y. CHEN[3], L.-Y. LU[3], ***M.-K. PAN**[2];
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Abstract: Our motor behaviors are built with extremely complex sets of ensembled muscle contractions in space and time. While motor preparation and initiation are widely studied, the neuronal mechanism to control motor kinematics, the temporal details of motor trajectories, remains largely unclear. Here we report that the olivocerebellum constructed motor kinematics by encoding instantaneous motor frequency. We started with single-unit and local field recordings in the freely moving *Grid2*^{dupE3} tremor mouse model. The tremor-frequency-related neuronal oscillations propagated in the cerebral-olivo-cerebello-thalamo-cortical circuit. Pharmacological thalamic and cerebellar silencing confirmed that frequency-dependent oscillations are generated within the olivocerebellar circuit. Single-unit analysis revealed that tremor frequencies are not generated at a single-cell level but require populational ensembles of neuronal firings that lead to cerebellar oscillations. We can generate tremors in wild-type mice by recapitulating the populational firing and cerebellar oscillations optogenetically within the olivocerebellum. We next studied volitional rhythmic movements. Using a vibrational platform to generate volitional compensatory movements, we confirmed that the same populational coding and cerebellar oscillations could be generated with matched motor frequencies in a wide frequency range of physiological movements. Optogenetic manipulations within the olivocerebellum reliably generated rhythmic movements with matched frequencies. Given that non-rhythmic motor behaviors can be constructed by constantly changing instantaneous frequencies, we applied both vibration platform and optogenetic manipulations with complex dynamics of chirp frequencies. The mice can generate complex cerebellar oscillations and complex motor kinematics with precisely matched frequency dynamics. In humans, we also confirmed the cerebellar mechanism in patients with essential tremor and healthy subjects using a wide range of neurophysiological techniques, including cerebellar electroencephalography (EEG), deep brain stimulation (DBS), transcranial alternating current stimulation (tACS) with surface electroencephalogram (EMG) or accelerometers. In summary, we identify that the olivocerebellum can construct motor kinematics by encoding instantaneous motor frequencies. This frequency coding mechanism is precise, linear, and real-time across every experimental mouse and human. This bottom-layer neuronal mechanism to encode motor kinematics may significantly impact motor control and brain-computer interface research.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.02/Y8

Topic: E.02. Cerebellum

Title: On-ubcs in the flocculus of the vestibulocerebellum stabilize gaze in the dark

Authors: *R. N. KOOPS[1], C. B. CANTO[1], P. SCHEIFFELE[2], B. H. J. WINKELMAN[3,1], C. I. DE ZEEUW[1,3];
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Abstract: The flocculus of the vestibulocerebellum contains a high density of unipolar brush cells (UBCs), the function of which remains to be elucidated. Dependent on their positive or negative response to presynaptic glutamate release, one can distinguish so-called ON-UBCs and OFF-UBCs, respectively. Here we studied the function of the ON-UBCs, which form the most dominant type in the flocculus and relay vestibular input signals to other UBCs and granule cells. Optogenetic ArchT-mice equipped with an amber LED on the left flocculus were used to study the effect of limiting ON-UBC activity on the vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR). Optogenetic inhibition of ON-UBCs elicited a horizontal drift of the ipsilateral eye towards the nasal side exclusively during the VOR in the dark. This drift, which depended on the intensity of optogenetic LED stimulation, was most prominent at higher peak velocities. No such large effects were observed in the phase or gain of the VOR. These results suggest that ON-UBCs in the flocculus are involved in vestibular, but not visual, compensatory eye movement control, stabilizing the eye position in the dark.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

Location: WCC Halls A-C

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Topic: E.02. Cerebellum

Support: NIH Grant DC014276
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Title: Regulations of Vestibulo-Ocular Reflex and Optokinetic Response by GABA-A and GABA-B Receptors in the Mouse Cerebellar Flocculus

Authors: C. YIN[1], F. HAMPTON[1], *T. YAKUSHEVA[2];
[1]Washington Univ. in St. Louis Sch. of Med., Saint Louis, MO; [2]Washington Univ. in St.Louis, Sch. of Medi, Saint Louis, MO

Abstract: The cerebellar flocculus (FL) is part of the vestibulocerebellum and is known to control vestibulo-ocular and optokinetic reflex (VOR and OKR, respectively). Although the FL neuronal connectivity is well understood, it is shocking that even for simple oculomotor behaviors like VOR, we still do not know the role of specific excitatory and inhibitory pathways within the FL. Most types of local circuit neurons in the FL are GABAergic and function via GABA-A and GABA-B receptors within all layers of the FL. Our previous study in primates has shown that blockage of GABA-A receptors in the vicinity of Purkinje cells changed neuronal responsiveness to oculomotor tasks without affecting the overall behavior. Specifically, injections of gabazine (GABA-A receptor antagonist) changed the spatial tuning of Purkinje cells during saccades and increased the neuronal gain to pursuit and VOR cancellation. These experiments did not affect the overall behavior because the area affected around the Purkinje cell was small, up to 300 microns. In this study, we blocked GABAergic transmission via large injections of GABA-A and GABA-B receptor antagonists to the ipsilateral side of FL in the alert-behaving mouse. We recorded mouse eye movements before and after drug applications. We used four paradigms: optokinetic stimulation, VOR cancellation, VOR in the light, and VOR in the dark. We found that injection of phaclofen (a potent GABA-B antagonist) in the flocculus decreased OKR and VOR gains at all tested frequencies, suggesting that this slow-acting inhibition modulates the gain of the output signal (PC response). Gabazine injections (a GABA-A antagonist) in the flocculus eliminated OKR behavior and increased eye movements during VOR (cancelation and VORd). We found that phaclofen induced longer-lasting gain changes than gabazine. Thus, GABAergic inhibition within cerebellar FL is essential for the normal functioning of OKR, VOR, and VOR adaption.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

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Topic: E.02. Cerebellum

Support: 1R37NS128416

Title: Neural control of tongue movements by the primate cerebellum

Authors: *P. HAGE[1], M. FAKHARIAN[2], I. JANG[2], V. LOOI[2], J. PI[2], S. P. OROZCO[2], E. SEDAGHAT-NEJAD[2], R. SHADMEHR[2];
[2]Biomed. Engin., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The cerebellum plays a critical role in control of tongue movements, as illustrated by the fact that cerebellar damage leads to impairments such as dysarthria. Yet, the way in which tongue kinematics are represented in the firing rates of cerebellar neurons remains a mystery. Here, we recorded Purkinje cell (PC) simple and complex spikes, and the activities of putative molecular layer interneurons (MLI), as marmosets performed targeted licking movements. We examined the temporal coordination of spikes among PCs, among putative MLIs, and between MLIs and PCs, asking whether their spikes synchronized during movements. We engaged two adult marmosets in a targeted licking task while recording from 105 definitively identified PCs, and from 138 putative MLIs, in lobule VI of the vermis. PCs were identified through the presence of complex spikes. Putative MLIs were identified using both spatial information relative to the PC layer, as well as their inhibitory interactions with identified PCs. We found that PC firing patterns in response to licking, for both simple and complex spikes, were broad: some neurons increased their baseline activity, while others decreased, oscillating at roughly the same frequency as that of licking and often ramping up prior to the initiation of a bout. Furthermore, they varied in their phasic relationship to a lick: specifically active during either protraction or retraction phases of a single lick. Notably, PC activity showed weak kinematic-specific changes in modulation. Critically, we observed that among pairs of PCs, the simple spikes exhibited direction specific synchronization particularly at the end of the lick's protraction phase. The putative MLIs, unlike PCs, uniformly increased their activity during licking bouts, with a ramping of activity beginning prior to the start of a bout. Their activity was modulated in phase with licking. However, unlike PCs, MLIs exquisitely scaled their activity with lick duration. Moreover, the strength of their inhibitory interactions with PCs was direction specific, and greater during a lick than during baseline. In summary, we identified lick-related regions of the cerebellar vermis of marmosets and utilized high-density electrodes to record from multiple PCs and MLIs simultaneously. We found that PCs tended to synchronize their simple spikes with each other, particularly as the tongue neared the end of its protraction phase. Unlike PCs, the MLIs exquisitely scaled their spike rates with lick duration, and increased the strength of their inhibition of PCs during licking, suggesting that they played a critical role in coordinating spike timing of PCs.

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Poster

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Topic: E.02. Cerebellum

Support: NIH Grant R01NS112917
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Title: Cell-type resolution of circuit computations in the cerebellum during smooth pursuit eye movements

Authors: *D. J. HERZFELD, S. G. LISBERGER;
Neurobio., Duke Univ., Durham, NC

Abstract: The floccular complex of the cerebellum plays a critical role in the execution of smooth pursuit eye movements. Here, we recorded 1,000+ neurons from the floccular complex of rhesus monkeys using multi-contact silicon probes, allowing us to link the activity of populations of identified neurons to performance in this exemplar sensorimotor behavior. We leveraged the well-known cerebellar circuit as well as machine learning techniques to label well-isolated neural units with their cell-type identities. We trained a probabilistic classifier using a subset of expert-labeled neurons whose identities were established through careful examination of spike waveforms, cerebellar layer, and auto- and cross-correlograms. As input to the classifier we provided: (i) raw waveforms, (ii) auto-correlograms stratified by the firing rate of the unit (3D-ACG), and (iii) layer information derived from local field potentials. The classifier demonstrated a cross-validated accuracy of approximately 90% in predicting withheld expert labels. Mossy fibers, the primary inputs to the cerebellar circuit, responded in relation to both the animal's eye position and velocity. Yet, Purkinje cells, the sole output of the cerebellar cortex, showed responses that depended on the animal's eye velocity and acceleration with little/no contribution of eye position. Thus, a fundamental computation by the floccular circuit is to convert position-sensitivity mossy fiber inputs to an output that is strongly related to velocity. The responses of the remaining neural populations suggest the locus of this transformation in the cerebellar circuit. Molecular layer interneurons (MLIs) showed strong eye velocity-dependent responses, with preferred directions of pursuit that were opposite simultaneously recorded Purkinje cells. Because MLIs receive inputs mainly from parallel fibers, we suggest that transformation of eye position into velocity signals occurs in the granule cell layer. Golgi cells showed little modulation, suggesting limited involvement in the position-to-velocity transformation. Unipolar brush cells showed stronger position-related responses than mossy fibers, consistent with their role in integration rather than differentiation. Overall, our findings underscore the critical role of granule cells as suppliers of velocity signals to both molecular layer interneurons and Purkinje cells. Our results highlight the significance of processing within the granule cell layer and indicate that granule cells are not merely relaying mossy fiber inputs to the cerebellar cortex.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

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Topic: E.02. Cerebellum

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Title: Locomotor phenotypes following graded ablation of Purkinje cells and granule cells in adult mice

Authors: *J. R. JACOBS[1], M. CAREY[2];
[1]Fundacao Champalimaud, Lisbon, Portugal; [2]Champalimaud Ctr. For the Unknown, Lisboa, Portugal

Abstract: The cerebellum is critical for the coordination and calibration of movement. Various theories have attempted to map distinct cerebellar sub-functions onto distinct cerebellar cell types. Here, we asked how ablation of select cerebellar neurons in adult mice affects specific quantitative features of locomotion and locomotor learning. We used a cre-recombinase mediated strategy to target diphtheria toxin receptors (DTR) to Purkinje cells or granule cells (in isolation or in conjunction with mossy fibers). Intraperitoneal injection of diphtheria toxin (DT) in adult mice then led to dose-dependent ablation of the respective neurons. We subsequently analyzed the resulting locomotor phenotypes during both overground walking and locomotor learning on a split-belt treadmill. We found that ablation across all cell types converged on an ataxic phenotype and locomotor learning deficits which were largely reflective of those seen in the Purkinje cell degeneration mutant mouse (pcd). Furthermore, the degree of both locomotor ataxia and impairments in locomotor learning scaled with the magnitude of cell death across both Purkinje cell and granule cell ablations. Finally, and perhaps surprisingly, our data suggest that both locomotion and locomotor learning may be more robust to loss of Purkinje cells than granule cells.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

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Portuguese FCT PD/BD/128291/2017 (AIG)
Portuguese FCT PD/BD/141643/2018 (DD)

Title: Faithful encoding of motor coordination by individual Purkinje cells

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Abstract: The cerebellum is critical for coordinating movement across the body; during locomotion it is particularly important for interlimb coordination. Decades of recordings have consistently shown that cerebellar Purkinje cell modulation is broadly correlated with the locomotor stride cycle. However, much of the firing rate variability has remained unexplained, and it is not yet clear how Purkinje cell activity could be read out to control whole-body coordination. Here, we performed cell-attached recordings to monitor Purkinje cell activity in head-fixed mice locomoting for liquid rewards, together with high-speed 3D tracking of limb, tongue and body kinematics. We then quantified the contributions of specific behavioral features to overall firing rate modulation using Generalized Linear and Additive Models. Our analyses reveal that beyond representing the locomotor stride cycle, Purkinje cells are exquisitely sensitive to stride-to-stride kinematic variation. Further, the vast majority of Purkinje cells simultaneously encode movements of multiple body parts to provide precise representations of temporal coordination across the body. Together, these two findings resolve much of the long-standing confusion surrounding the role of Purkinje cells in locomotor control. Moreover, the high prevalence of non-linear mixed selectivity across the Purkinje cell population could allow for efficient readouts of whole-body coordination by a simple linear decoder, explaining how the cerebellum flexibly coordinates interlimb and whole-body movements in dynamic environments.

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Poster

PSTR085. Cerebellum: Circuits and Behavior

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.08/Y15

Topic: E.02. Cerebellum

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Title: A dual Purkinje rate and synchrony code sculpts movement kinematics

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Abstract: Studies in human and animal subjects emphasize the importance of the cerebellar output to the online control of ongoing movement and cerebral cortical states. The cerebellar

GABAergic Purkinje cells (PC) are the main controller of the cerebellar output. Given the high PC firing rate, they place the cerebellar output neurons in the nuclei under constant inhibition, as such, a decrease in their rate during behavior is correlated with many behavioral kinematics. PC synchrony on the other hand, is an understudied mechanism that was also shown to increase nuclear firing.We aimed to probe the role of PC synchrony in behavior. To achieve this, we recorded the extracellular activity of 404 putative PCs in 7 mice reaching for food- using Neuropixels probes. We then calculated the synchrony index (SI) between the simultaneously recorded PCs. SI was defined as the probability of finding a spike in two PCs in 1ms time bin, divided by the probability of finding a spike in each PC individually, for the same time window. This index was related to different movement kinematics to uncover the direct role of PC synchrony in cerebellar computations and behavior.We found a significant increase in synchrony of PCs that drop their rate during behavior. This increase is beyond what can be expected based on the drop in firing rate alone. During behavior, the trial-to-trial changes in synchrony were positively correlated with deceleration and negatively correlated with the endpoint position, i.e. higher synchrony led to faster deceleration and undershoot of the target. Importantly however, combining the synchrony with the firing modulation was better correlated with the behavioral kinematics than each code individually. In the past, PC synchrony was suggested to increase the nuclear firing, still, the way this is dictated remains obscure. To address this, we built a computational model and found that higher PC synchrony limits the time duration where the nuclear cells are inhibited by the PCs, allowing for more time where the nuclear cells can be active. In line with this, ex vivo dynamic clamp experiments showed that combining both PC firing with synchrony better recapitulate the firing rate that was observed in the nuclear cells of behaving animals in the past.Our data suggest that PC synchrony is an important mechanism that is utilized by PCs to enhance their signal transmission to the nuclear cells, this code works in cahoots with the firing modulation to rapidly control nuclear firing and movement kinematics, suggesting a dual signaling code from PCs to downstream elements.

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Poster

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Topic: E.02. Cerebellum

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Title: The role of cerebellar output in the control of motor coordination and learning

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Abstract: The cerebellum performs feedforward motor control facilitated by error-driven, temporally precise learning, which relies upon mechanisms of associative learning. These principles enable the cerebellum to exert anticipatory control upon movements and to adapt to predictive errors. Lesions to the output of the cerebellum, the anterior interposed nucleus (IntA), are characterized by endpoint dysmetria and previous work from the lab identified a causal role of IntA output on limb deceleration. However, IntA contains multiple cell types with diverse targets that previous electrophysiological investigations did not fully isolate. Using an intersectional genetics approach, we isolated cell-type and pathway-specific populations in Vglut2-cre mice that project to the red nucleus (RN). Closed-loop optogenetic activation of IntA-RN neurons during reach decelerated the outward movement, consistent with effects seen with less constrained opsin expression. Next, we performed high density neural recordings in the IntA and used antidromic optogenetic stimulation from RN to optically identify IntA-RN neurons. We found that the neuronal activity in these cells was tightly aligned to reach endpoint and the firing rate scaled with deceleration. These findings demonstrate that IntA-RN neuronal activity precedes and controls the decelerative component of ongoing reaching movements, consistent with an anticipatory controller. This observation leads to a question however: if the cerebellum both corrects and controls movements, would erroneous control from its output engage its own corrective mechanisms? To address this, we tested whether repeated reach perturbations induced with closed loop optogenetic activation of IntA-RN neurons drive learning. No evidence of within-block adaptation was observed when stimulating IntA at a positional threshold during every trial, in contrast with what we previously observed when stimulating cerebellar mossy fiber inputs on each trial. Reach kinematics remained perturbed by the optogenetic stimulation, with effects equivalent at early and late phases of the block. We wondered whether this effect indicated a lack of learning or obstruction of the expression of learning. To address this, we examined trials after the stimulation block for evidence of after-effects. Modest and short-lived aftereffects were seen early in the washout block, with higher peak velocities observed at the time of stimulation onset. These findings suggest that learning is occurring upstream of the IntA, likely in the cerebellar cortex, and that stimulation of the IntA blocks the expression, but not the acquisition, of learning.

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Poster

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Title: Activity in cerebellar Purkinje cells during sensorimotor adaptation for manual interception

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Abstract: The cerebellum has widely been thought to play a key role in motor adaptation through error-driven learning, in which error information is encoded in complex spikes of Purkinje cells to adjust internal representations carried by simple spike activity. However, recent studies indicate that information processing of cerebellar learning is more diverse and complicated than conventionally thought. In the present study, we recorded single-neuron activity of Purkinje cells in the lateral cerebellum while rhesus monkeys performed a manual interception task, in which a visual target moved along a circular path at different speeds for an unpredicted duration (cue), and then was occluded by a mask for a fixed duration (occlusion). The monkeys were then required to intercept the target within a limited time after the GO cue appeared, as indicated by the dimmed central-fixation spot. Feedback for both the touch position and the actual target location would be displayed as two dots in different colors. During the adaptation block, the angular position of the target would shift forward during the occlusion to induce a sensorimotor adaptation. We found that simple spike activity of most Purkinje cells was tuned to reaching direction during pre- or peri-movement periods; meanwhile about half the cells showed modulation with the target location during the cue period. During the adaptation, simple-spike activity exhibited learning-dependent changes around the GO cue and after feedback onset. On the other hand, complex-spike activity was directionally tuned to upcoming movements at a relatively fixed timing (200 ms before GO cue), during which we assume a specific motor plan was formed. Furthermore, complex spikes occurring at that time would change the tuning strength of simple-spike activity of the same neuron. These results suggest that Purkinje cells in the lateral cerebellum are involved in the control and learning of visually guided arm movements. In particular, complex spikes predict motor kinematics and adjust information encoded by simple spikes of the same neuron, while simple-spike activity reflects the process of adaptation learning.

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Poster

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Title: Cerebellar lesions disrupt feed-forward and feedback control during visually guided reaching.

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Abstract: The cerebellum is known to play an important role in the coordination and timing of limb movements. The present study focused on how reach kinematics are affected by cerebellar lesions to quantify both the presence of motor impairment, and recovery of motor function over time. In the current study, 12 patients with isolated cerebellar stroke completed clinical measures of cognitive and motor function, as well as a visually guided reaching (VGR) task using the Kinarm exoskeleton at baseline (~2 weeks), as well as 6, 12, and 24-weeks post-stroke. During the VGR task, patients made unassisted reaches with visual feedback from a central 'start' position to one of eight targets arranged in a circle. At baseline, 6/12 patients were impaired across several parameters of the VGR task compared to a Kinarm normative sample (n=307), revealing deficits in both feed-forward and feedback control. The only clinical measure that consistently demonstrated impairment was the Purdue Pegboard Task (PPT). Overall, patients who were impaired at baseline showed significant recovery by the 24-week follow-up for both VGR and the PPT. A lesion overlap analysis indicated that the regions most commonly damaged in 5/12 patients (42% overlap) were lobule IX and Crus II of the right cerebellum. A lesion subtraction analysis comparing patients who were impaired (n=6) vs. unimpaired (n=6) on the VGR task at baseline showed that the region most commonly damaged in impaired patients was lobule VIII of the right cerebellum (40% overlap). Our results lend further support to the notion that the cerebellum is involved in both feedforward and feedback control during reaching, and that cerebellar patients tend to recover relatively quickly overall. In addition, we argue that future research should study the effects of cerebellar damage on visuomotor control from a perception-action theoretical framework to better understand how the cerebellum works with the dorsal visual stream to control visually guided actions.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Program #/Poster #: PSTR086.01/Y19

Topic: E.03. Basal Ganglia

Title: Automatic analysis of locomotor bout frequency, vigor, and complexity among mice with GPCR Smoothened loss and gain of function in cholinergic interneurons

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Abstract: Locomotion, a fundamental behavior, is classically assessed using simple metrics of velocity and total distance moved in an open field. This behavior however offers rich data about the organization and breadth of actions an animal can take while only facing limitations due to the bio-mechanical constraints of the organism. Importantly, these actions are not biased towards a particular task-solution space imposed by many behavioral paradigms. Here, to analyze motor complexity in freely ambulating mice, we developed a method for the automatic and unbiased identification of locomotor bouts which we call bout finder (BF). This analysis utilizes open field data to derive and quantify 24 locomotion parameters.To test BF sensitivity we benchmarked it against previously established methods. BF was then applied to examine locomotor differences between mice with selective gain and loss of GPCR Smoothened (Smo) function in cholinergic interneurons (CINs). CINs are the main source of striatal Acetylcholine and are critical for action switching. Our group also previously demonstrated that the activation or ablation of Smo can impinge on CIN physiology. Basic open field analysis showed that mice with constitutively active Smo signaling selectively on CIN (SmoM2) moved less overall and at reduced average speeds compared to controls. However, BF analysis revealed that the nature of these differences was due to reduced number and duration of locomotor bouts longer than 0.5s among SmoM2 animals versus controls. Within these bouts, mean velocity, max velocity, distance traveled, average acceleration, max acceleration, and average number of acceleration inversions were all reduced while time to max velocity was increased. These differences were not observed among bouts shorter than 0.5s. The overall differences in locomotion observed between control and SmoM2 mice is therefore due to a deficit reaching higher velocities and initiating locomotor bouts among SmoM2 animals. In contrast, ablation of Smo selectively from CIN produced no difference in gross distance moved and mean velocity compared to controls. However, application of BF revealed a significant difference in time to maximal speed within bouts longer than 0.5s. Specifically, CIN-specific Smo ablation animals showed reduced average time to max velocity within bouts suggesting a bidirectional effect of Smo activity on locomotor complexity. Together, these results not only validate our novel bout detection method for the analysis of rich naturalistic locomotion, but also reveal bidirectional changes in locomotor complexity following manipulations to Smo on CIN.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Topic: E.03. Basal Ganglia

Support: G-RISE T32GM136499
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CUNY ASRC IRG 2021

Title: The orphan receptor GPR139 modulates cholinergic activity in the striatum

Authors: D. ZUELKE[1], **N. GENTILE**[2], K. STEPHENS-JONES[3], A. WALLS[4], S. URIBE-CANO[5], *A. KOTTMANN[6];
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Abstract: Cholinergic interneurons (CIN) are critically involved in reinforcement learning. Specifically, they integrate information streams carried by glutamate from cortex and thalamus. Importantly, their activity is also modulated by over 40 different signals that impinge on acetylcholine (ACh) release via G protein coupled receptors (GPCRs). One of those is the GPCR Smoothened (Smo). We recently found that Smo signaling is required for maintaining expression of the orphan GPCR GPR139 in CIN. GPR139 expression in the wild-type striatum reveals a prominent low (medial) to high (lateral) expression gradient suggesting a possible involvement in reinforcement learning. Furthermore, GPR139 has been recently shown to be a negative modulator of endo-opioid signaling acting downstream of mu-opioid receptor (MOR) activation by morphine and fentanyl. Morphine decreases ACh release, while antagonists of MOR increase striatal ACh. Since pausing ACh release is critical for the reinforcing action of dopamine (DA), we hypothesize that Smo and GPR139 signaling impinges on reinforcement learning via regulating ACh release dynamics. To test this hypothesis, we use fiber photometry with AAV GRAB sensors for DA and ACh to monitor extracellular levels of DA and ACh in the striatum of mice with loss and gain of function of Smo signaling combined with Smo and GPR139 specific pharmacology. Our preliminary results indicate that GPR 139 increases ACh release. Further, consistent with an increase in cholinergic activity we observe that activation of Smo counteracts place preference formation. We are currently investigating whether Smo and GPR139 pharmacology alter reciprocal release dynamics of DA and ACh.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Program #/Poster #: PSTR086.03/Z1

Topic:

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Title: Angiotensin Converting Enzyme 2 (ACE2) activity impacts cholinergic physiology in the dorsolateral striatum

Authors: *A. R. WALLS[1,3], S. URIBE-CANO[2,3], D. ZUELKE[1,3], L. J. LEE[3], A. H. KOTTMANN[3];
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Abstract: A recent study showed that SARS-CoV2 virus particles can persist in the mesencephalic dopamine neurons (DAN) of patients who died without detectable virus in the periphery. Given the role of ACE2 as the SARS-CoV2 viral receptor, this and other findings support the expression of membrane integrated ACE2 in the basal ganglia. While ACE2 is known to be a carboxy mono peptidase, its exact role in basal ganglia function is not well understood. Interestingly, ACE and ACE2, which respectively process angiotensinogen into the cell stress promoting peptide AngII and AngII into the neuroprotective peptide Ang1-7, are expressed in opposite gradients along the medial to lateral axis of the striatum, the main input structure to the basal ganglia. Specifically, ACE presents a medial-low to lateral-high pattern of expression suggesting greater prevalence of stress promoting AngII in the lateral striatum while ACE2 presents a medial-high to lateral-low pattern suggesting a greater prevalence of neuroprotective Ang1-7 in medial regions. Using deep sequencing of affinity purified mRNA, we find co-expression of the stress promoting AngII receptor AT1R and the neuroprotective Ang1-7 receptor MasR in striatal cholinergic interneurons (CIN), the main source of striatal Acetylcholine (ACh) and a neuronal population key for reinforcement learning, behavioral flexibility, and striatal plasticity. This suggests cellular stress among CIN might be bidirectionally modulated through changes in ACE and ACE2 activity. In support of this hypothesis, we observe that inhibiting ACE2 with the clinically used ACE2 inhibitor MLN4760 reduces the amplitude of Acetylcholine (ACh) burst release measured by fiber photometry in the lateral striatum. Conversely, the ACE2 agonist DIZE increases the amplitude of ACh burst release. Currently, we use enzyme activity based MALDI imaging to quantify AngII and Ang1-7 across striatal domains and test if ACE2 activity impinges on the characteristically high levels of physiological cell stress in CIN and supports neuronal long-term maintenance. Further, since DAN are known to express angiotensinogen, our experiments suggest the intriguing possibility that co-released angiotensinogen, together with DAN expressed ACE2 could impact cholinergic physiology in response to dopamine in a striatal domain specific manner.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Topic: E.03. Basal Ganglia

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Title: Activation of the GPCR Smoothened Modulates Striatal Acetylcholine by Impinging on Cholinergic Interneuron Physiological Cell Stress

Authors: *S. URIBE-CANO[1], A. CHOUDHURY[1], N. M. CORDERO[2], M. A. KADIR[2], A. H. KOTTMANN[1];
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Abstract: Dopamine (DA) and Acetylcholine (ACh) levels in the Striatum are key for regulating the local plasticity which underlies reinforcement learning. Evidence suggests that the relative balance of these two neurotransmitters emphasizes either direct or indirect pathway output from the Striatum. Specifically, elevated DA promotes direct pathway signaling which produces motor output while elevated ACh promotes indirect pathway signaling to arrest motor output. While DA afferents from the midbrain act as the main source of Striatal DA, Cholinergic Interneurons of the Striatum (CIN) act as the main source of ACh. The dynamics of these two neurotransmitters are also linked given that DA transients promote a “pause” in CIN burst firing through activation of Gai-coupled DA2 receptors (DR2). This reduction of CIN activity produces a window of low ACh release during which DA-dependent plasticity of glutamatergic synapses on direct pathway medium spiny neurons can take place. Interestingly, a recent study found that inhibition of CIN by DA via DR2 is sensitive to changes in CIN physiological cell stress. More specifically, Helseth and colleagues found that CIN have uniquely elevated baseline levels of physiological cell stress as measured by phosphorylation of eukaryotic translation initiation factor 2A (p-eIF2a), a property that when suppressed appears to invert D2R action and cause D2R-mediated excitation of CIN. This observation suggests that factors impinging on CIN cell stress may be capable of modulating CIN response to DA, the balance of Striatal ACh and DA, downstream motor output, and Striatal plasticity at large. We previously observed that CIN in the adult Striatum crucially depend on the signaling peptide Sonic Hedgehog (Shh) for long-term survival. In addition to its role as a morphogen, Shh also impinges on markers of ER stress and cAMP levels through activation of the downstream requisite GPCR Smoothened (Smo). However, the acute effects of Smo activation on CIN and whether it can modulate DR2 activity via impingement on CIN physiological cell stress remains unclear. In the work presented here we examine how changes to CIN cell stress mediated by Smo impact DR2 signaling. Specifically, we utilize immunohistochemistry to characterize the impact of Smo activity on p-eIF2a across CIN of different Striatal sub-compartments and of different embryonic origins. Then, utilizing fiber photometry alongside genetically encoded GRAB-ACh sensors, we examine how Smo and DR2 pharmacology in combination with CIN-Specific ablation of Smo or DR2, as well as CIN-specific expression of SmoM2 (a constitutively active form of Smo), impacts striatal ACh release dynamics.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Topic: E.03. Basal Ganglia

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Title: Cortical innervation of the Subthalamic Nucleus and Zona Incerta in monkeys: Differential origin and patterns of connectivity

Authors: *A. GALVAN[1], N. MAGNUSSON[1], A.-C. MARTEL[1], V. BARRAGAN[1], N. M. BOULIS[2], T. FEDERICI[2], Y. LAKHINA[2], Y. SMITH[1];
[1]Emory Natl. Primate Res. Ctr., [2]Dept of Neurosurg. and Translational Neurosci. Core, Emory Univ., Atlanta, GA

Abstract: Pyramidal tract layer V neurons in the primary motor cortex are the main source of descending motor commands through the corticospinal tract (CST). Although there is evidence that efference copies of this descending information is transmitted to various subcortical regions via axon collaterals, the extent of these collateralized projections remains poorly known. In this study, we took advantage of the unique axonal transport properties of AAV2-retro to determine if the CST is the main source of axon collateral projections to the subthalamic nucleus (STN) and the zona incerta (ZI) in rhesus monkeys. In contrast to traditional retrograde tracers that label exclusively the somatodendritic domain of projection neurons, the axonal branching of retrogradely transduced cells with AAV2-retro is profusely labeled allowing for the analysis of their efferent connectome. Based on single cell filling studies, the current view is that cortical projections to the STN and the ZI largely originate from collaterals of the CST. However, given the limited number of neurons analyzed in these studies, the generalization of data to the population of corticofugal neurons must be done with caution.
In the present study, we injected AAV2-retro-hSyn-GFP in the lower cervical spinal cord of rhesus monkeys, which resulted in massive Golgi-like, retrograde labeling of pyramidal neurons in the arm-related region of M1 and prominent labeling of the CST. We measured the densitometry of GFP terminal/axonal labeling in the STN and ZI to determine the extent of their respective CST collateral innervation. The difference in the intensity of GFP labeling between the two regions was striking. While only sparse GFP-labeled terminal profiles were found in the lateral tier of the STN, the latero-ventral part of the ZI was massively innervated by CST collaterals. On the other hand, when cortical projections were identified by anterograde labeling after AAV5-hSyn-GFP injections in the arm region of M1 (3 animals), both the dorsolateral region of the STN and the latero-ventral area of the ZI were invaded by rich plexuses of GFP-

labeled terminals.
These preliminary data suggest that a significant contingent of the cortical innervation to the STN may not originate from axon collaterals of the CST, but rather arises from a specific subset of cortico-subthalamic neurons. In contrast, the bulk of cortical motor inputs to the ZI likely comes from axon collaterals of the CST. Work is in progress to confirm these preliminary results in additional monkeys and compare the ultrastructural features and pattern of synaptic connectivity of cortical terminals between the STN and the ZI using electron microscopy.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

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Title: Morphological plasticity of corticofugal neurons associated with the progressive development of parkinsonism in MPTP-treated monkeys

Authors: *R. M. VILLALBA[1], Y. LAKHINA[2], T. FEDERICI[2], N. M. BOULIS[2], A. GALVAN[3], **Y. SMITH**[3];
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Abstract: In Parkinson’s disease (PD), dysfunction of the basal ganglia-thalamo-cortical loops induced by striatal dopamine (DA) disrupts processing in the primary motor cortex (M1) and supplementary motor area (SMA). Although both cortical regions are involved in motor control, they play specific functions; M1 being involved in movement execution and motor learning, while SMA is related to planning and coordination of internally generated movement sequences. Our recent studies have shown reduced thalamocortical innervation of deep cortical layers in both motor cortical areas and loss of spines on M1 pyramidal neurons. Because these findings were obtained from parkinsonsian monkeys with severe striatal DA depletion, it is unclear when these cortical abnormalities develop and how they relate to the emergence of parkinsonism. In the present study, we will use healthy animals and MPTP-treated monkeys at different stages of striatal DA denervation to assess the temporal progression of neuroplastic alterations in different

populations of corticofugal pyramidal neurons in M1 and SMA. The pyramidal neurons have been identified by injections of the retrogradely transported viruses AAV2-retro in the spinal cord, lower medulla, or the putamen. Following injections in three control monkeys, both M1 and SMA were enriched in Golgi-like retrogradely labeled pyramidal neurons allowing for morphometric analysis of their cell body, dendritic length, complexity of dendritic arborization and spine density using Neurolucida and Neurolucida Explorer (MBF Bioscience,VT-USA). Preliminary data obtained so far from control monkeys indicate: (1) layer V corticospinal, corticomedullary and corticostriatal pyramidal neurons in M1 have a larger soma size and a more complex and extensive basilar dendritic tree as well as a larger density of dendritic spines than corticofugal neurons in SMA and (2) differences in the overall layer distribution and morphology of corticomedullary/corticospinal vs corticostriatal neurons in M1 and SMA suggest that they largely form two distinct populations of corticofugal neurons in primate motor cortices. Ongoing studies in MPTP-treated monkeys with different stages of striatal DA depletion are in progress. A deeper understanding of the circuit pathophysiology of specific populations of cortical pyramidal neurons in parkinsonism will lead, potentially, to the design of therapeutic approaches to modulate the activity of specific subsets of cortical pyramidal neurons in PD.

Disclosures: R.M. Villalba: None. **Y. Lakhina:** None. **T. Federici:** None. **N.M. Boulis:** None. **A. Galvan:** None. **Y. Smith:** None.

Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.07/Z5

Topic: E.03. Basal Ganglia

Support: NIH UDALL Center grant P50NS1223
ASAP; NIH/ORIP P51OD011132
ASAP-020572

Title: Development and evaluation of deep learning algorithms for assessment of cortical neuronal mapping in control and MPTP-treated Parkinsonian Monkeys

Authors: *G. J. MASILAMONI[1,2], J.-F. PARE[1,2], S. JENKINS[1,2], N. M. BOULIS[3], T. FEDERICI[3], Y. LAKHINA[3], A. GALVAN[1,2,4], Y. SMITH[1,2,4];
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Abstract: In primates, layer V pyramidal neurons in the primary motor cortex (M1) and the supplementary motor area (SMA) are the main sources of motor control information to several subcortical structures including the spinal cord, medulla, striatum, thalamus, hypothalamus, and brainstem nuclei. Although these projections have long been recognized and studied in detail in

isolation, much remains to be known about their exact cellular origin. A specific key question that remains to be addressed is whether they originate from individual pyramidal neurons, or if they share a common origin that send efference copies to multiple subcortical targets via axon collaterals. Recent findings suggest that there is a high level of heterogeneity and species differences in the extent of axon collateralization of individual pyramidal tract neurons between primates and rodents (Sinopoulou et al., 2022, Neuron 110:1-14). As part of an ongoing research program that aims at elucidating neuroplastic changes in the morphology and axonal connections of M1 and SMA corticofugal neurons in parkinsonian monkeys, we used AAV2-retro to map and compare the cortical distribution, morphology and changes in the efferent connectome of corticospinal, corticostriatal, and cortico-medulla neurons between control and parkinsonian monkeys. Given the large size of the rhesus monkey brain and the wide distribution of retrogradely labeled cells, there is need for an accurate, efficient and reproducible automated approach to map the distribution of labeled cortical neurons in these animals. Although traditional stereological cell counting techniques could be used for this purpose, they are extremely laborious, time-consuming, and even often vary between individual raters. To overcome this problem, we developed a deep learning neural network-based model to quantify and map the distribution of immunoperoxidase-stained cortical neurons using cloud-based Aiforia platform (Penttinen et al., 2018, EJN 48:2354). The algorithm was trained to detect immunoreactive cortical neurons and exclude the pyramidal tract fibers, terminals, blood vessels, and any artifacts generated during tissue processing and image acquisition. The results of the image analysis model were verified and replicated by 3 expert neuroscientists before being released and applied to all animals used in our studies. Our findings demonstrate that the neural networks algorithm and fully cloud embedded Aiforia™ platform provide an efficient and fast analysis of the distribution and relative abundance of corticofugal neurons in normal and parkinsonian monkeys.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

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Topic: E.03. Basal Ganglia

Support: NIH grant P51OD011132
ASAP-020572

Title: Collateral Projections of Corticostriatal Neurons in Primates: A Main Source of Inputs to the Pontine Nuclei and High-order Thalamic Nuclei

Authors: B. KIM[1], J.-F. PARE[1,2], S. JENKINS[1,2], Y. SMITH[1,2,3];
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Abstract: Although layer V pyramidal neurons are the main sources of cortical inputs to subcortical structures including the spinal cord, medulla, pons, thalamus, and various brainstem regions, it remains unclear as to whether these various targets receive inputs from single or segregated populations pyramidal tract (PT) neurons. The lack of efficient tools to characterize the full axonal arbor of specific populations of PT neurons in primates has significantly hampered progress in this area. The recent introduction of the recombinant adeno-associated virus serotype 2 (AAV2-retro), with highly potent and selective retrograde transduction properties, addresses some of these limitations. Our findings demonstrate that AAV2-retro is a highly reliable tool to retrogradely label the full somatodendritic domain and axon collaterals of corticostriatal neurons in rhesus monkeys, allowing for the analysis of the efferent connectome of these cells. Following AAV2-retro injections in the post-commissural putamen (sensorimotor territory) of rhesus monkeys, Golgi-like retrogradely labeled layer V cortical neurons were found throughout various motor and somatosensory cortices as well in non-motor parietal regions. These striatal injections also resulted in labeling of axon terminal profiles in various subcortical nuclei not known to receive direct projections from the striatum. In particular, high order thalamic nuclei such as the mediodorsal nucleus and pulvinar as well as the pontine nuclei (PN) were enriched in clusters of large varicose terminal-like profiles. Given that the bulk of retrogradely labeled cells in these animals were found in the cerebral cortex, we hypothesized that labeled terminals in PN and thalamus originated from collaterals of corticostriatal axons. In line with this possibility, preliminary electron microscopy data from two monkeys showed that PN axon terminals form asymmetric (putatively excitatory-glutamatergic) synapses with dendritic profiles and express vGluT1, a specific marker of cortical terminals. These results suggest that PN, and possibly the pulvinar and mediodorsal thalamic nuclei, receive efference copies of signals sent to the striatum, thereby providing routes through which sensorimotor corticostriatal information can reach various brain regions, including the cerebellum. Further work will determine how these connections are altered in a nonhuman primate model of PD.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

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Program #/Poster #: PSTR086.09/Z7

Topic: E.03. Basal Ganglia

Title: Msn d1 morphology features across transcriptomic types in the mouse striatum

Authors: *J. ANDRADE WILSON, S. WALLING-BELL, L. ALFILER, G. WILLIAMS, M. MALLORY, R. DALLEY, S. SORENSEN;
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Abstract: Medium spiny neurons (MSNs) make up over 90% of neurons in the striatum (Chuhma et al., 2011) and play an important role in motor behavior, including motor skill learning (Liang et al., 2022). MSNs are the principal target of excitatory cortical and thalamic inputs that converge in the striatum. These GABAergic cells are distinguished by their expression of dopamine receptors D1 or D2, and a high density of spines (Zhou, 2020). MSN D1 neurons, components of the direct pathway, and MSN D2 neurons, components on the indirect pathway, have functionally distinct roles. Generally, D1 and D2 MSNs have been thought to be homogenous in their somatodendritic morphology, but one study has shown that MSN D1 has more primary dendrites as well as a higher number of branch points and terminal endings than MSN D2 (Gertler et al., 2008). Transcriptomic descriptions of cell types provide a universal framework to discuss the diversity of cell types in the brain. The newly released mouse whole brain transcriptomic taxonomy, a comprehensive atlas based on transcriptomic and spatial cell type data (Yao et al., 2023), maps MSN D1 cells to 33 transcriptomic types (t-types) across the basal ganglia. Here, we investigate whether there are dendritic differences across t-types within the MSN D1 subclass. Neurons from the MSN D1 t-types were sampled in the Nucleus Accumbens and Caudoputamen using the Patch-seq technique. Cells were either manually reconstructed in a three-dimensional environment using the Mozak module of Vaa3D software, or automatically reconstructed by automated methods followed by manual edits. Next, we analyzed the morphological features of these neurons, finding shifts in the number of dendritic branches and the distribution of dendrite density relative to the soma across select t-types. Based on these results, and an expanding dataset, we aim to further explore morphological feature differences between MSN t-types including investigating the relationship of MSN D1 t-type morphology and their spatial location across the dorsal and ventral striatum.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

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Topic: E.03. Basal Ganglia

Support: NIH Grant UM1MH130981
NIH Grant UF1MH128339

Title: Patch-seq reveals morpho-electric differences and regional contrasts in primate striatal cell types

Authors: *X.-P. LIU, N. JOHANSEN, R. DALLEY, J. MILLER, M. WIRTHLIN, T. BAKKEN, S. SORENSEN, T. JARSKY, J. T. TING, H. ZENG, E. LEIN, B. LEE, B. E. KALMBACH;
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Abstract: The basal ganglia are a set of subcortical nuclei that contribute to motor control, motor learning, and motivated behavior. Quantifying cellular diversity in the basal ganglia is crucial for understanding its function as well as its dysfunction in neurodegenerative disorders, addiction, and other neuropsychiatric conditions. While there is a wealth of knowledge about the properties of basal ganglia cell types in rodents, less is known regarding primate basal ganglia cell types. Despite the evolutionarily ancient nature of the basal ganglia and basic circuitry, recent single cell RNA-seq studies (Krienen et al., 2020; He et al., 2021) have pointed to novel cell types present in the primate but not murine striatum (the input nuclei to the basal ganglia) as well as divergent gene expression in conserved types. Furthermore, these studies suggest that there is substantial diversity in the transcriptomically-defined cellular repertoire, but it is unclear how this diversity relates to diversity in properties like intrinsic electrophysiology and morphology. To this end, we applied Patch-seq in non-human primate (Macaca nemestrina and Macaca mulatta) striatum brain slices obtained from local tissue distribution programs to obtain triple-modality (electrophysiological, transcriptomic, and morphological) data. We tested for differences in the morpho-electric properties of various principal medium spiny neuron (MSN) and interneuron types, including $TAC3^+$ interneuron and MSN types reported in primates but not mice. To target rare cell types, like cholinergic interneurons, we applied viral tools in slice culture to fluorescently label cell types of interest. We found that features including spike width, input resistance, afterhyperpolarization, and I_h-related sag varied across cells. Some of this diversity stemmed from transcriptomic type - for instance, a prevalent PVALB-expressing interneuron subclass had gene expression and electrophysiological properties consistent with fast spiking, while other interneuron subclasses were not as strikingly fast spiking. A second source of diversity related to regional axes of variation, such as that corresponding to the topographic cortico-striatal projections from motor, sensory, associational, and limbic areas. Indeed, MSN-like neurons of the dorsal striatum had electrophysiological properties that differed from those of ventral striatum, which may support their respective participation in motor control versus reward processing. Through these data, we hope to better understand the relationship between gene expression, electrophysiology, and function, as well as refinements from mouse to primate.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.11/Z9

Topic: E.03. Basal Ganglia

Title: Correspondence of transcriptomic and electrophysiological properties along spatial axes in basal ganglia

Authors: *A. BUDZILLO, C. LEE, R. DALLEY, R. MANN, N. JOHANSEN, J. A. MILLER, B. TASIC, H. ZENG, B. E. KALMBACH, S. SORENSEN, Z. YAO, B. R. LEE, N. GOUWENS;
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Abstract: The interconnected subcortical structures known as the basal ganglia are critical for mediating executive function and the learning and control of voluntary behaviors across species. Evidence for topographical architecture and presence of spatial axes and subdomains within these structures is thought to enable information processing in parallel loops. In addition, there is a growing appreciation of the diversity of transcriptomic cell types (t-types) in these structures. To investigate the correspondences between transcriptomic identity, intrinsic electrophysiological properties, and cell position in the basal ganglia, we generated Patch-clamp data from the nucleus accumbens, caudoputamen, globus pallidus (GP), subthalamic nucleus (STN), and substantia nigra pars reticulata (SNr) in brain slices from the adult mouse. We measured electrophysiological properties by whole-cell patch clamp recordings and collected the nucleus and cytosol upon completion for RNA-seq analysis. We used the cells' transcriptional profiles both to assign t-types from a mouse whole-brain taxonomy and also to uncover continuous transcriptomic gradients in the expression of highly variable genes within broader transcriptomic groups. Finally, we mapped the cells' locations within the brain using the standardized Allen Common Coordinate Framework. Cells from the striatum, GP, SNr, and STN exhibit distinct electrophysiological properties, and we find evidence for aligned continua of transcriptomic and electrophysiological properties within these structures. For example, medium spiny neurons (MSNs) exhibit transcriptomic variation along the ventromedial-dorsolateral axis, which correlates with electrophysiological differences such as the depth of the action potential after-hyperpolarization. We also find t-types with unusual electrophysiological properties and use marker gene expression to identify them as a recently described ventromedial population of striosome-like D2+ MSNs expressing Htr7 and Th. In addition, we applied non-negative matrix-factorization to MERFISH data for each basal ganglia structure and identified spatial patterns associated with specific groups of t-types; several of these groups exhibit particular physiological properties. These data characterize discrete and continuous variation in transcriptomic signatures and phenotypes of the basal ganglia and suggest ways in which specialized populations of neurons contribute to processing topographically organized information.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

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Topic: E.03. Basal Ganglia

Support: NIH F31 NS124343-02
NIH R01NS094450
NSF IOS-1845355

Title: Anatomical Mapping and Functional Plasticity of Sensory and Motor Corticostriatal Projections to Striatal Spiny Projection Neurons and Fast-Spiking Interneurons

Authors: *B. SANABRIA[1], S. BASKAR[1], A. J. YONK[2], C. R. LEE[1], D. J. MARGOLIS[1];
[2]Cell Biol. and Neurosci., [1]Rutgers Univ. Grad. Program In Neurosci., Piscataway, NJ

Abstract: The striatum, a key input structure of the basal ganglia, contributes to sensorimotor learning by sorting information about our surroundings, actions, and rewards. Part of the complexity of the striatum derives from the anatomical and functional organization of its neuronal circuitry. Corticostriatal projections from the primary sensory (S1) and motor (M1) cortex converge in the dorsolateral striatum and evoke cell-type specific responses in striatal spiny projection neurons (SPNs) and parvalbumin fast spiking interneurons (FSIs). The mechanism underlying the integration of S1 and M1 by SPNs and FSIs remains unclear however, activity in striatal neurons is largely dependent on the timing and combination of inputs from local and distant neurons. Thus, we hypothesized that there are distinct differences in the number and distribution of S1 and M1 projections onto SPNs and FSIs and their capacity for long term potentiation (LTP). To anatomically map S1 and M1 synapses onto SPNs and FSIs, AAVs expressing Ruby2 or GFP spaghetti monster fluorescent proteins (sm.FP) were injected into both S1 and M1. Ex vivo whole cell current clamp recordings of striatal neurons with biocytin was used to label individual neurons and confocal z-stacks images were acquired. 3D reconstructions of S1 and M1 projections innervating our biocytin filled neurons were created using Imaris software. Puncta from S1 and M1 making close approximations (<0.5µm) to the edge of our filled neurons were quantified as putative synapses and their distribution along the entirety of the neuron was calculated. To test for cell-type specific differences in the capacity for LTP, we injected AAVs expressing channelrhodopsin 2 (ChR2) into S1 and M1. Ex-vivo current clamp recordings of striatal neurons were performed while optogenetically stimulating M1 or S1 terminals with a theta burst stimulation (TBS) pattern, which is enhanced during learning and potentiates corticostriatal synapses. The average amplitude of postsynaptic potentials generated by a single pulse stimulus before and after TBS was compared. Our anatomical results strongly indicate that SPNs receive a significantly greater number of synaptic contacts from M1 than from S1. In contrast, no significant differences between the average number of contacts from M1 and S1 were found in FSIs. Similarly, M1 and S1 synapses in FSIs were equally potentiated by TBS. Our results suggest that cell-type specific differences in the innervation by M1 and S1 has functional implications on synaptic plasticity and sensorimotor integration in striatal neurons.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

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Title: Motor cortex projects monosynaptically to neurons of the substantia nigra pars reticulata

Authors: *W. THOMPSON, S. GRILLNER, G. SILBERBERG;
Neurosci., Karolinska Institutet, Solna, Sweden

Abstract: The basal ganglia are a set of subcortical brain nuclei, fundamental to volitional motor control. In the rodent brain, the substantia nigra pars reticulata (SNr) is the primary output stage of the basal ganglia. GABAergic SNr neurons are tonically active and inhibit a number of targets throughout the brainstem and diencephalon. Inputs from other basal ganglia nuclei shape the firing patterns of SNr neurons, changing the degree of inhibition passed on to downstream targets. Recent anatomical evidence has shown that axons originating in the motor cortex emit collaterals at the level of the SNr (Foster et al., 2021; Yang et al., 2023). However, a functional connection between motor cortex and SNr neurons remains unexplored. Using a virally-targeted optogenetic approach, we photostimulated axon terminals from the motor cortex, while performing whole cell patch-clamp recordings of SNr neurons in acute brain slices of adult mice. We show that GABAergic SNr neurons receive input from the motor cortex and confirm, via pharmacology, that this input is monosynaptic. We characterised the glutamate receptor composition of the motor cortex-SNr synapse and found that the post synaptic response was mediated primarily by AMPA receptors. Furthermore, we demonstrate that photostimulation of these cortical axon terminals can significantly increase SNr neuron firing rate beyond baseline. To further investigate the spatial organisation of cortical input to SNr, we employed a transsynaptic viral-labelling approach to tag SNr neurons that receive monosynaptic input from motor cortex. While SNr neurons receiving monosynaptic input from motor cortex were observed along the rostrocaudal extent of the SNr, along the mediolateral axis they were concentrated in the lateral two-thirds of the nucleus. We further employed this technique to observe the output targets the SNr neurons that receive input from motor cortex. We identified labelled axons in a number of known SNr targets. This finding reveals a functional pathway by which motor cortex can directly activate SNr - bypassing other basal ganglia nuclei - to further increase inhibition of downstream targets. This newly identified source of input to SNr was incorporated into an *in silico* model for further analysis into its functional role.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.14/Z12

Topic: E.03. Basal Ganglia

Support: NARSAD Young Investigator Award
K99 Pathway to Independence Award NINDS

Title: Granular circuit configuration of direct parallel striatopallidal projections to thalamus and brainstem revealed by brain-wide mapping and single nucleus RNA sequencing

Authors: Z. GU[1], A. MENDELSOHN[1], ***L. NIKOOBAKHT**[1], J. LI[1], L. HAMMOND[1], E. THOMAS[2], C. RIMORIN[2], D. BERTAGNOLLI[2], M. TIEU[2], J. GOLDY[2], K. SMITH[2], B. TASIC[2], R. M. COSTA[2];
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Abstract: The basal ganglia play a critical role in deciding on appropriate actions and their timely execution. The classical model of basal ganglia function posits that the external globus pallidus (GPe) is a singular, homogeneous population of neurons acting as a relay in the striatopallidal pathway to inhibit movements. However, our recent research challenges this notion by revealing the remarkable heterogeneity of GPe neurons and their role as outputs of the striatopallidal pathway. Considering the well-established parallel nature of the striatopallidal pathway, it is plausible that striatal spiny projection neurons expressing D2 dopamine receptors can establish highly parallel output circuits through individual GPe subpopulations. This configuration allows for the direct transmission of motor, limbic, and associative cortical information to downstream targets in the thalamus and brainstem, thereby facilitating actions. In this study, we utilize anterograde tagging techniques to identify the parafascicular (Pf) thalamic and pedunculopontine (PPN) nuclei that receive direct input from GPe, enabling the visualization of their projections throughout the brain. Our findings elucidate that these subcircuits exhibit a significant degree of parallelism while displaying certain biases. Specifically, GPe-Pf subcircuits predominantly target discrete cortical areas and the striatum, whereas GPe-PPN subcircuits primarily project to various brainstem areas and spinal cords, thereby forming open D2-GPe-PPN-brainstem/spinal cord pathways. To gain further insight into the functional specialization of PPN neurons receiving GPe inputs (PPN^{GPe}), we employ a combination of single-cell and projection-defined single-nucleus RNA sequencing. This comprehensive approach enables the identification of distinct cell types within the PPN^{GPe} population based on neurotransmitter profiles and gene expression patterns. Surprisingly, our analysis reveals the existence of 34 transcriptomic cell types, including 13 clusters of glutamatergic neurons, 17 clusters of GABAergic neurons, and 1 cluster of cholinergic neurons. These findings suggest that the highly parallel and open GPe-PPN subcircuits possess the capability to simultaneously process multiple streams of information through functionally specialized subpopulations of PPN neurons. Overall, our results provide novel insights into the highly parallel yet distinct direct striatopallidal projections to the thalamus and brainstem that go beyond the classical direct and indirect model of basal ganglia function.

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Poster

PSTR086. Basal Ganglia: Connectivity, Cellular Identity, and Function

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.15/Z13

Topic: D.04. The Chemical Senses

Support: 2021ZD0204500

Title: A novel group of mesencephalic excitatory neurons contribute to multisensory integration and motor coordination within single cells

Authors: ***Y. LI**[1,2], Y. YANG[1,3], Y. WANG[1,2], X. DU[1,2], J. DU[1,2,3];
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Abstract: Linking the structural information with physiological functions is a key step toward a deeper interpretation of the nervous system. The current approach is to target specific neural circuits involved in well-developed stereotypical behaviors. In our study, we propose a new strategy to explore the relationship between neuronal structure and function using the mesoscopic whole-brain connectomic atlas. Based on our previously constructed brain-wide mesoscopic atlas with neuron identities, we identified a cluster of mescencephalic excitatory neurons (termed POEMs) in the pretectum with individual cells innervating the primary sensory olfactory epithelium and terminating in multiple motor-related regions. Based on their morphology, we hypothesized that POEMs may mediate coordinated motor outputs in response to specific sensory stimuli. Functional experiments confirmed that POEMs responded to various chemical and visual stimuli. Meanwhile, activating POEMs could induce contralateral tail-flick responses. We are now investigating the functional downstream circuits underlying POEM-induced movements. In summary, our work not only identifies a new type of mesencephalic excitatory neurons for multisensory-integration-to-motor transformation but provides a neomethodology of neural circuitry research.

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Poster

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Program #/Poster #: PSTR086.16/Z14

Topic: D.04. The Chemical Senses

Support: Giovanni Armenise-Harvard Career Development Award
EMBO Postdoctoral Fellowship

Title: Sniff-invariant concentration encoding in the primary olfactory cortex

Authors: A. A. DEHAQANI[1], F. MICHELON[1], L. PETRUCCO[1], P. PATELLA[1], E. PIASINI[3], ***G. IURILLI**[2];
[1]Inst. Italiano di Tecnologia, Rovereto, Italy; [2]Inst. Italiano di Tecnologia, Genova, Italy; [3]Intl. Sch. for Advanced Studies (SISSA), Trieste, Italy

Abstract: Our movements affect sensory measurements without our noticing it. How nervous systems distinguish these perturbations and maintain a stable representation of the world remains unclear. In olfaction, changing the speed of an inhalation changes the concentration of odors inside the nose. However, how fast an animal breathes in does not affect the perception of odor intensity. We discovered that the mouse's olfactory cortex has inhalation-invariant representations of odor concentration. This is because cortical neurons also encode the airflow rate inside the nose, affording a downstream brain area to track and discard the effect of inhalation-dependent concentration changes. Integrating independent mechanosensory feedback and external sensory information may be a canonical strategy that sensory systems deploy to mitigate ambiguity caused by the movement of sensory organs.

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Poster

PSTR087. Interlimb and Bimanual Control

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Title: Associations between resting and task-related γ-aminobutyric acid and Glx levels and 4 weeks of bimanual motor learning

Authors: *M. HEHL[1,2,3], S. VAN MALDEREN[2,1,3], S. P. SWINNEN[1,3], K. CUYPERS[2,3,1]; [1]KU Leuven, Leuven, Belgium; [2]Hasselt Univ., Diepenbeek, Belgium; [3]Leuven Brain Inst. (LBI), Leuven, Belgium

Abstract: Introduction. Most everyday tasks require well-coordinated bimanual movements, necessitating practice to initiate neuroplastic processes at the level of the brain for skill improvement. It is assumed that changes in excitatory and inhibitory neurometabolism are the precondition to allow for an increase in neural communication, which in turn might facilitate changes in functional and structural connectivity, and finally an improved motor performance. **Aim.** Here, we aimed to examine whether changes in neurometabolites can be associated with bimanual motor learning over 4 weeks. We investigated (1) changes in resting-state neurometabolite levels of the right and left primary sensorimotor cortex (R-/L-SM1) and left dorsal premotor cortex (L-PMd) with motor learning; and (2) task-related modulations of neurometabolites in L-PMd and modulation changes with motor learning. **Methods**. 63 young healthy adults participated in either a challenging or an easy (n = 33/30) 4-week bimanual motor task training paradigm and were scanned at baseline (BL), and after 2 and 4 weeks of motor training to test changes in neurochemicals across 3 time points. Using a 3T magnetic resonance (MR) scanner, we acquired anatomical T1-weighted images and MEGA-PRESS edited MR spectroscopy (TR/TE: 2000/68 ms) to obtain γ-aminobutyric acid (GABA) and combined glutamate-glutamine (Glx) levels for R- and L-SM1 at rest (voxel: 27 ml; 112 ON/112 OFF spectra), and for L-PMd in a dynamic manner (4 acquisition blocks of 11 min each: 1 x pre, 2 x during, 1 x post task performance; voxel: 25 ml; 160 ON/160 OFF spectra). Analyses were performed using Gannet (v3.3.1). **Results.** Task performance significantly improved between measurement sessions ($p < 0.0001$) and more for the challenging as compared to the easy training group ($p < 0.0116$). No changes in GABA with motor training or during task performance in the scanner could be observed. However, resting Glx levels in R-SM1 increased from BL to week 2 ($p = 0.0049$). For L-SM1, an interaction effect between training difficulty and measurement session could be observed ($p = 0.0182$), which however did not yield any significant *post hoc* effects. For L-PMd, only the challenging but not the easy training group showed a decrease in Glx towards week 4 when pooling the 4 acquisition blocks of L-PMd ($p < 0.0007$). There was no effect of task performance in the scanner on Glx levels. **Conclusion.** Bimanual motor training is associated with changes in Glx but not GABA levels of motor-related brain regions. Earlier evidence also suggested changes in GABA with motor training. However, these subtle differences might be region specific or only detectable using high-field MR spectroscopy.

Disclosures: M. Hehl: None. **S. Van Malderen:** None. **S.P. Swinnen:** None. **K. Cuypers:** None.

Poster

PSTR087. Interlimb and Bimanual Control

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Title: Temporal patterns of muscle activity and coordination revealed in frontoparietal cortex by intracortical microstimulation (ICMS)

Authors: *M. HAFEZI[1], J. A. LIGGINS[1], I. S. CHOW[1], J. K. DODD[1], L. A. GROCHOWSKI[1], A. L. BERGER[1], D. PADRES[3], B. K. NG[1], A. LANG-HODGE[1], S. R. U[2], D. F. COOKE[1]; [1]Biomed. Physiol. and Kinesiology, [2]Psychology, Simon Fraser Univ., Burnaby, BC, Canada; [3]Physiol., McGill Univ., Montréal, QC, Canada

Abstract: Motor behaviors involve coactivation of muscles with coordinated temporal patterns of activation. How the brain controls patterned muscle activity is not well-understood. We and others have shown that long-train intracortical microstimulation (LT-ICMS) in the motor cortex (M1) and surrounding fields evokes multi-joint movements resembling natural behaviors (eating, reaching, etc.). Manipulating inhibition within the defensive motor module selectively alters defensive responses without affecting other motor functions, highlighting the specific role of the module in that behavior. This evidence suggests that artificial LT-ICMS-evoked movements convey useful information about cortical motor control. Here we investigate the diversity and topography of temporal patterns in muscle activity evoked by LT-ICMS the frontoparietal cortex. We combine high-resolution ICMS mapping of whole-body topography with electromyography (EMG) to create maps of muscle representation. We applied long-train (500 ms) ICMS, consisting of biphasic pulses, to M1 and primary somatosensory cortex (S1) in anesthetized rats while recording video and EMG from 28 muscles across six rats and up to 16 muscles per rat. ICMS site density was moderately high with as many as 163 sites tested in one animal. Many ICMS movements were complex and multi-jointed, and some resembled specific behaviors like running/digging. ICMS-evoked muscle activation was observed in a variety of waveform profiles ranging from brief and short-latency to tonic and prolonged to complex multiphasic patterns. Initial latencies ranged from ~20-450 ms, and some sites evoked inhibition and/or excitation just after ICMS offset. EMG waveforms were compared within and across muscles based on their onset latency and their profile. In one case, 12 muscles were coactivated by ICMS at one site with evoked movements of the elbow, hip, and ankle. Hindlimb muscles showed initial latencies ranging from 40-150 ms. Individual muscle representations varied in shape and could be contiguous, distributed (with intervening EMG-negative sites), or bimodal, with two distinct clusters of sites. In some cases, there was a clear somatotopy of EMG waveforms evoked by ICMS across the cortex and surroundings. For instance, the trapezius representation was bimodal in both rats in which it was fully tested. ICMS in the caudolateral cluster, located in S1, evoked a distinct activity pattern, with brief spikes of activation in one rat and similar spikes combined with longer activation in the other rat in contrast to mostly tonic activity during ICMS in the rest of the representation.

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Poster

PSTR087. Interlimb and Bimanual Control

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.03/Z17

Topic: E.04. Voluntary Movements

Support: Natural Science and Engineering Research Council (NSERC)

Title: Functional Brain Networks for Unimanual and Bimanual Grasping: A Graph Theory Approach

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Abstract: Bimanual grasping is assumed to be more complex than unimanual grasps due to the demands of coordination and synchronization between both limbs (e.g., Kelso et al., 1979). Previous studies suggest that right parietal areas for left-hand grasping also show specialization for bimanual grasping (Le et al., 2014, 2017, 2019) and that decoded cortical activation for bimanual grasp is more similar to left versus right grasp (Guo et al., 2021). Based on these factors, we hypothesized that functional cortical networks for bimanual grasp would be more fully ‘connected’ (especially bilaterally) than for unimanual grasp, and would resemble left more than right hand grasp networks. To test this, we conducted a secondary analysis of visually guided unimanual and bimanual grasping tasks recorded via a 64-channel EEG in 15 right-handed participants (see in Guo et al., 2021). The experimental paradigm consisted of three types of grasps: left-hand grasping, right-hand grasping (both using the thumb and index finger), and bimanual grasping (using the index fingers of both hands). Each trial involved participants viewing an object for 500-1000ms, followed by an auditory Go cue indicating the grasping type. We selected 250ms EEG segments aligned with the Go cue for Graph Theoretical Analysis (GTA), calculating measures of functional topology and dynamics such as node clustering, network efficiency, and brain modularity. Overall, bimanual grasping resulted in a small-world network with significantly higher values of clustering coefficient and global efficiency, suggesting faster and more efficient information processing compared to unimanual conditions. Modules derived from electrodes over frontal-parietal and occipital areas were identified for each grasping condition, with the bimanual condition involving more electrodes from the frontal area. Consistent with our hypotheses, left-hand grasping and bimanual grasping both showed extensive bilateral ‘frontoparietal connectivity’ patterns, whereas right-hand ‘connectivity’ was more restricted to the left hemisphere. Overall, these data confirm an increased bilateral

information sharing and a specialized role for the left (non-dominant) hemisphere in bimanual grasp.

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Poster

PSTR087. Interlimb and Bimanual Control

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Topic: E.04. Voluntary Movements

Support: Grand-in-Aid (KAKEN) from the Japan Society for the Promotion of Science (JSPS) 20J21594

Title: Comparison between lower-limb corticospinal facilitation during upper-limb muscle contractions and upper-limb corticospinal facilitation during lower-limb muscle contractions

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Abstract: One phenomenon that represents the neural interaction between the human upper and lower limbs is interlimb corticospinal facilitation, which is the facilitation of corticospinal excitability of the upper or lower limb by lower- or upper-limb, respectively, voluntary muscle contractions. Interlimb corticospinal facilitation is assumed to be the neural basis of interlimb coordination. However, despite differences in the functional roles of the human upper and lower limbs, lower-limb corticospinal facilitation during upper-limb muscle contractions (upper-to-lower CF) and upper-limb corticospinal facilitation during lower-limb muscle contractions (lower-to-upper CF) have not been compared. Therefore, this study examined the differences in interlimb corticospinal facilitation from the upper to lower and lower to upper limbs. Eighteen healthy adults participated in the experiment (5 females, 24.1 ± 3.2 years old). Transcranial magnetic stimulation was applied to the left primary motor cortex (M1) to obtain motor evoked potentials (MEPs) which reflect the corticospinal excitability of a recorded muscle. We measured single pulse MEPs from the right tibialis anterior (TA) muscle at rest or during voluntary right flexor carpi radialis (FCR) muscle contractions for upper-to-lower CF and single pulse MEPs from the right FCR muscle at rest or during voluntary right TA muscle contractions for lower-to-upper CF. Muscle contraction intensity was set at 30% of the maximum voluntary contraction force. In addition to single pulse MEPs, short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF) at rest or during homolateral muscle contraction were measured to compare intracortical mechanisms of the M1 in interlimb corticospinal facilitation. Results showed that there was no significant difference between upper-to-lower CF and lower-to-upper CF (upper-to-lower CF: 244 ± 171% (median - 173%), lower-to-upper CF: 185 ± 95%

(median - 161%), $t_{(17)} = 1.08$, $p = 0.29$). In addition, there was no significant difference in the modulation of SICI and SICF by homolateral muscle contraction between upper-to-lower and lower-to-upper ([SICI] upper-to-lower: 151 ± 83%, lower-to-upper: 129 ± 83%, $t_{(17)} = 0.87$, $p = 0.40$; [SICF] upper-to-lower: 150 ± 78%, lower-to-upper: 141 ± 50%, $t_{(17)} = 0.03$, $p = 0.97$). Note that statistical tests were performed using log-transformed values to ensure a normal distribution, but nonparametric statistical tests showed similar results. These results indicate that interlimb corticospinal facilitation does not reflect differences in the functional roles of human upper and lower limbs.

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Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

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Topic: E.04. Voluntary Movements

Support: HKRGC-GRF 14102221
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HKRGC-GRF 14113522

Title: Inter-limb transfer of novel motor skill in mouse

Authors: X. YANG[1], S. WANG[1], Y. KE[1], *W. YUNG[2];
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Abstract: Novel motor task training with unilateral limb results in automatic gain of performance in the untrained limb in humans. Despite the robustness of this inter-limb transfer phenomenon in various behavioral tests, the underlying neural mechanisms are still unclear. Taking advantage of the rodent model that allows reliable tracking of the same neuronal ensemble in the motor cortex by multi-photon imaging during the training process, we developed a forelimb task to explore the inter-limb skill transfer phenomenon and mechanism. Significant improvements were witnessed in general motor performance as well as refined kinematic characteristics for the untrained limb of mice after repeated practice with the other limb. At neuronal level, unilateral practicing induced gradual cortical adaptations not only in the contralateral hemisphere but also in the ipsilateral hemisphere that was supposed to control the resting limb only. Remarkably, in corpus callosum bisected mice, although the ability of unilateral motor learning was maintained, their inter-limb transfer phenomenon became inconspicuous. Meanwhile, evolvement of population level activities of the primary motor cortex on the ipsilateral side was also altered. These data suggested cross activation of the untrained limb during unilateral training and indicated a key role of the transcallosal pathway in transferring learned motor memory to the opposite hemisphere.

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Poster

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Topic: E.04. Voluntary Movements

Support: Research Project A, the Center for Global Studies on Culture and Society, College of Economics, Nihon University

Title: Coordination dynamics between visual stimulus and unimanual circle movements

Authors: *T. MURAOKA[1], D. TAKESHITA[2];
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Abstract: The coordination dynamics of unimanual movements in response to visual stimulus have been considered to be constrained similarly to the intra-person coordination dynamics of interlimb movements. The coordination is stable at a relative phase difference of 0° (in-phase) and 180° (anti-phase), and the stability is high in in-phase. It is difficult to maintain coordination in phases other than in-phase and anti-phase. In most of the previous studies, reciprocating visual stimuli were used and there was no restriction on gaze shift. Since the salient point of reciprocal motion, i.e., turnover, affects the coordination dynamics, it is possible that the coordination dynamics would be different in circular motion without salient points. In addition, because information exchange between the left and right cerebral hemispheres affects the coordination dynamics, the coordination dynamics when a visual stimulus is presented in one visual field and its contralateral limb moves may be different from that when the gaze shift is not allowed. Therefore, we conducted an experiment to clarify the coordination dynamics when a circularly moving visual stimulus is presented in the left visual field and the right hand moves in a circular motion in coordination with this visual stimulus. A fixation point O and a point P moving in a circular motion at 0.5 Hz were shown on a monitor. Subjects (N=17) gazed at O. The task of moving the right hand in coordination with P consisted of four conditions: moving the hand 90° ahead of P (+90° condition), moving in-phase (0° condition), moving the hand 90° behind P (-90° condition), and moving in anti-phase (180° condition). The results showed that the 0° condition was more stable than the +90° and 180° conditions. In addition, the 0° and -90° conditions were more accurate than the +90° and 180° conditions. These results differed from the previous results in that no difference was found in the coordination dynamics in 180° and +90° condition, and that no difference was found between 0° and -90° condition. The former may be due to the floor effect caused by the higher task difficulty. In the latter case, the visual stimuli in the -90°condition may have functioned as a target to reach and facilitated predictive control.

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Poster

PSTR087. Interlimb and Bimanual Control

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Topic: E.04. Voluntary Movements

Support: NIH P20GM103449

Title: The neural basis of the contextual interference effect in young adults

Authors: *H. M. SISTI, R. BALCHA, G. FREITAS, E. VARGAS;
Norwich Univ., Northfield, VT

Abstract: The neural basis of learning is a central question of neuroscience. It has important implications for brain health and human development. The contextual interference (CI) effect is a learning phenomenon whereby the type of practice schedule influences long-term retention. The CI effect compares blocked and randomized schedules. In blocked, participants practice one task variant per day, whereas in the randomized schedule, participants practice all task variants each day. Despite the same amount of practice, acquisition is superior in the blocked group, however, long-term retention is superior in the randomized group. In the present study, we used a visuomotor tracking task coupled with EEG to elucidate the neural dynamics of this learning phenomenon. For each trial, participants were asked to track a moving dot along a jagged line by rotating left and right dials. The starting point was either the bottom, top, or left-side of the screen. In the blocked condition (n=20), the starting point remained constant during each practice session. In the randomized condition (n=16), the starting point was randomized. A novel Pre-Test (wavy line) was done immediately before the first day of practice; Post-Test was done approximately one week after the end of training. EEG data were collected during the first and last days only. We hypothesized that those who practiced the jagged line task with the randomized schedule would demonstrate better retention, despite poorer performance during acquisition. Performance was assessed by measuring the Euclidean distance between the participant's cursor and the target at the end of a trial (Finish Offset). An ANOVA was calculated to determine the effect of condition (Blocked vs. Random) and session (Pre vs. Post). The 2 x 2 ANOVA revealed a significant main effect of condition ($F=7.19$, $p < .01$) and a significant main effect of session ($F=31.57$, $p<.001$), but no significant interaction of Condition x Session, ($F=1.07$, $p=0.30$). These data suggest that learning did occur in both groups, however the hypothesis of a significant interaction was not supported. It is most likely that the task variants were not sufficiently different to induce the contextual interference phenomenon. EEG analysis is currently underway.

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Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.08/Z22

Topic: E.04. Voluntary Movements

Title: The Effect of Posture on Corticospinal Excitability of Trunk Muscles during Rhythmic Arm Movements

Authors: A. PEARCE, M. TAYLOR, ***S.-Y. CHIOU**;
Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Background: Unilateral voluntary contractions of muscles of the upper limbs increase corticospinal excitability of trunk muscles in humans, a phenomenon known as crossed facilitation. However, the modulation of rhythmic, bilateral upper-limb movements on the corticospinal excitability of the trunk muscles in healthy adults remains unknown. **Objectives:** The study aimed to investigate the crossed facilitation in the erector spinae (ES) of the trunk during rhythmic bilateral arm cycling and whether position of the trunk influenced the degree of facilitation. **Methods:** Fifteen adults underwent the study. Transcranial magnetic stimulation (TMS) applied over the primary motor cortex was used to elicit motor evoked potentials (MEP) in the ES during rhythmic arm cycling and during voluntary trunk extension in a seated position with and without the torso supported. Peak-to-peak amplitudes of MEPs in the ES obtained during arm cycling and voluntary trunk extension were measured to reflect the corticospinal excitability of the ES. Additionally, short-interval intracortical inhibition (SICI) and cervicomedullary MEPs (CMEPs) were evaluated in a subset of the participants during the arm cycling and voluntary trunk extension to measure the motor cortical and spinal excitability. **Results:** MEP amplitudes of the ES were greater during the arm cycling than during the voluntary trunk extension when the torso was supported (168.06±75.48% of ES MEPs during trunk extension) and unsupported (119.24±34.91%). SICI was decreased during the arm cycling (55.35±10.85%) compared to the trunk extension (44.08±10.04%). In contrast, the CMEP amplitudes of the ES were increased during the trunk extension compared to during the arm cycling (124.19±17.84% of ES CMEPs during arm cycling). **Conclusions:** Rhythmic bilateral arm cycling movements facilitated corticospinal excitability of the ES and the facilitatory effect was present when the torso was supported and unsupported. Additionally, the facilitatory effect induced by the arm cycling is likely mediated by the motor cortical circuits. Our findings suggest a simple rehabilitation method for inducing neuroplasticity in the pathways projecting to the trunk muscles for clinical populations with impaired trunk control, such as spinal cord injury.

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Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR087.09/Z23

Topic: E.04. Voluntary Movements

Support: 1 F31 NS129336-01A1

Title: A class of bilateral corticospinal neurons induces symmetric movements

Authors: *B. FAIT[1], B. COTTO[1], T. MURAKAMI[1], H. ZHAN[2], M. HAGEMANN-JENSEN[3], O. STEWARD[4], N. HEINTZ[1], E. SCHMIDT[1];
[1]Lab. of Mol. Biol., Rockefeller Univ., New York, NY; [2]MAPseq/BARseq Core Facility, Cold Spring Harbor Lab., Cold Spring Harbor, NY; [3]Karolinska Institutet, Solna, Sweden; [4]Univ. of California Irvine, Univ. of California Irvine, Irvine CA, CA

Abstract: The spinal cord receives dense inputs from the motor cortex (Kuypers, 1981). While predominantly a contralateral projection, a minority of axons project to the hemisphere of the spinal cord ipsilateral to their cortex of origin (Armand, 1982). While these projections are well-investigated in the context of injury recovery, their naturalistic function is unknown (Alawieh et al., 2017; Martin, 2005). First, we analyzed the post-synaptic projectome of the ipsilateral and contralateral portions of the corticospinal tract using a combination of monosynaptic anterograde tracing and Smart-Seq3 single nucleus sequencing (Hagemann-Jensen et al., 2020). We found that the ipsilateral tract projects potently to motor-involved interneurons, while the contralateral tract projects primarily to sensory-involved interneurons. With viral barcode-based single neuron projection reconstruction (Kebschull et al., 2016), we mapped the tract and found evidence for a class of bilateral, bifurcated corticospinal neurons comprising the majority of ipsilaterally-projecting fibers (Fig 1A-C). They occupy a distinct cortical topography, and deep transcriptomic characterization with viral TRAP profiling revealed a suite of differentially-expressed axonal guidance molecules involved in spinal midline crossing (Nectow et al., 2017). To investigate their function, we optogenetically stimulated these bifurcated neurons in anesthetized animals and found they induce bilateral and symmetric limb movements, whereas stimulating the corticospinal tract as a whole induced only unilateral movements (Fig 1D-E). Together, we propose that this class of genetically-defined bilateral corticospinal neurons represents a potentially generalizable circuit structure for the descending coordination of symmetrical motor behavior.

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Poster

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Program #/Poster #: PSTR087.10/Z24

Topic: E.04. Voluntary Movements

Title: Effects of motor imagery on lower limb muscle corticospinal excitability for various motor actions

Authors: *K. ISHIKAWA, N. KANEKO, K. NAKAZAWA;
Univ. of Tokyo, Tokyo, Japan

Abstract: Motor imagery (MI) is known to induce neural activities in the central nervous system related to actual movement and has been applied in clinical practice as an effective rehabilitation method. Previous studies on the upper limb muscles demonstrated that corticospinal excitability (CE) of the target muscle was increased when the target muscle was an agonist muscle in the imagined motor tasks. When the target muscle was imagined as an antagonistic muscle, the reported modulation of the CE was controversial. In the present study, we aimed to clarify whether the CE of the target muscle would be increased or decreased when the target muscle plays as an antagonistic muscle in MI tasks. Fifteen healthy adults participated in this study. The electromyographic signal was recorded from the rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and soleus (SOL) muscles of the right leg. CE was assessed with motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation to the primary motor cortex. The optimal stimulation spot was set at the location where the largest MEP could be recorded from the RF muscle. The stimulus intensity was set at 120% of the motor threshold. MEPs were recorded at rest and during four different MI tasks. In the rest task, participants were asked not to imagine anything and not to contract their muscles. In the MI tasks, they were asked to imagine 1)knee flexion, 2) knee extension, 3) ankle plantar flexion, and 4) ankle dorsiflexion without muscle contraction. The results showed that MEP amplitudes in the RF muscle were significantly increased during MI of the knee extension, ankle plantar flexion, and ankle dorsiflexion ($p < 0.05$), but not during knee flexion, compared to the rest task. In the TA muscle, MEP amplitudes were significantly increased during MI of the knee extension and ankle dorsiflexion ($p < 0.05$), but not during ankle plantar flexion. In the SOL muscle, MEP amplitude during any MI task was not significantly different from those during the rest task. While the reported CE modulation was controversial in the previous studies on upper limb muscles when the target muscle was imagined as an antagonistic muscle, the present result demonstrated no CE changes when the target muscles were antagonistic muscles in the MI tasks. Further studies are needed to explore potential variations in the effects of motor imagery on changes in excitability within the corticospinal tracts for both upper limb and lower limb muscles, considering the different neural control mechanisms governing these muscle groups.

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Poster

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Title: Interlimb coordination of stretch reflex during bimanual postural maintenance task by interhemispheric inhibition

Authors: *H. SUGINO[1], J. USHIYAMA[2,3];
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Abstract: When the left and right limbs need to be coordinated such as carrying a tray, a cooperative reflex response occurs in the long latency reflex (ex. Dimitriou et al. 2012). However, in our daily life, the left and right limbs were often used independently. This study shows the existence of default interaction in the long latency reflex even in situations where each arm needs to be controlled independently.Twelve participants performed a bimanual postural maintenance task in experiment 1. Participants maintained their upper limb posture under background load, where elbow flexion perturbation was given to the right elbow, left elbow, or both elbows at random orders and timings. During unilateral perturbation, participants were required to keep the unperturbed limb in the starting position under background load. Electromyogram activities were recorded from both sides of the triceps brachii muscle (TB) and were divided into three components of stretch reflex with reference to the timing of perturbation (R1, 20-50 ms; R2, 51-75 ms; R3, 76-105 ms). The results of experiment 1 showed that the stretch reflex was elicited in the perturbed limb in all tasks, while the TB activity in the unperturbed side was decreased in the R2 period compared to the baseline, despite the unperturbed limb being required to maintain its start position. Next, twelve participants performed experiment 2 to investigate the mechanism behind the inhibited activity in the unperturbed limb observed in experiment 1. Transcranial magnetic stimulation (TMS) was applied to the left primary motor cortex corresponding to the right TB hotspot in time with the long latency component of the stretch reflex, with the intensity set at the active motor threshold. As a result of the TMS application, the long latency reflex was enhanced during right hand perturbation. This result was consistent with findings from a previous study (Palmer & Ashby, 1995), and suggested that the primary motor cortex is responsible for long latency reflex. Moreover, motor evoked potentials (MEPs) of the right TB during left perturbation were reduced compared to MEPs during the postural maintenance alone. This result indicated that corticospinal excitability of the unperturbed limb was inhibited in R2 by left perturbation.These findings suggest a default interaction between the left and right limb stretch reflexes, even when separate task demands are required for each limb. Since the long latency reflex is assumed to originate from the primary motor cortex, the inhibition of the unperturbed limb would be the result of interhemispheric inhibition associated with the primary motor cortex activity of the perturbed limb.

Disclosures: H. Sugino: None. **J. Ushiyama:** None.

Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.12/Z26

Topic: E.04. Voluntary Movements

Title: The role of visual information in bimanual reaching and grasping movements in Virtual Reality

Authors: *G. DE CELLIO MARTINS[1], B. J. SPECHER[2], C. M. MILLER[3], A. MASON[4]; [1]Kinesiology, Univ. of Wisconsin, Madison, Madison, WI; [2]Inst. for Discovery, [3]Kinesiology, [4]Univ. of Wisconsin - Madison, Madison, WI

Abstract: Reaching and grasping are some of the earliest developing motor skills in humans, and our interaction with objects is facilitated by the strategic use of visual feedback. However, the sensorimotor mechanisms involved in prehension are incredibly complex. For example, when reaching with both hands simultaneously to laterally positioned objects, it is not possible to obtain continuous visual information about both objects. Visual attention must be allocated effectively across both hands and both targets. Biases in the allocation of visual attention towards either the dominant or non-dominant hand/target may thus be a factor in how bimanual movements are coordinated. We conducted the current study on the effects of different forms of visual occlusion on bimanual prehensile behavior. This type of study has previously been incredibly difficult to perform because precisely occluding either the body or aspects of the environment has been a considerable challenge. Virtual reality (VR) provides an effective tool to control what and when visual information is available to the participant. Therefore, the purpose of this study was to determine how upper limb movement patterns within VR are influenced by the presence or absence of visual feedback about one or both hands throughout the reach to grasp movement. Twenty right-handed healthy young adults (12 female, M = 23.35 ± 3.2 years) participated in this study. Participants wore a fully immersive HTC VivePro VR headset and performed bimanual reaching and grasping movements to same-sized small virtual cubes (3cm) under four different visual feedback conditions: A) Graphic feedback about both hands visible; B) Graphic feedback about the right hand occluded; C) Graphic feedback about the left hand occluded and D) Graphic feedback about both hands occluded. Participants performed 20 trials per condition. The condition with graphic feedback about both hands was always completed first, whereas the order of the three occlusion conditions was counterbalanced between participants. There were fewer errors with the right-hand overall. Results indicated that the number of errors (missing the cube with one or both hands) was significantly higher when both hands were occluded or when the left hand was occluded compared to full-vision (*ps* <0.05). For both single occlusion conditions, the number of errors was significantly higher for the occluded hands in comparison to the non-occluded (*ps* <0.05). These two findings seem to indicate that precision during prehensile movement is affected by the lack of vision of one or two hands and that participants divide their visual attention to execute precise grasps.

Disclosures: G. de Cellio Martins: None. **B.J. Specher:** None. **C.M. Miller:** None. **A. Mason:** None.

Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.13/Z27

Topic: E.04. Voluntary Movements

Title: Control of bimanual lifting of symmetric and asymmetrically loaded objects

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Abstract: Previous studies of bimanual lifting have focused on anticipatory control of hand forces and placement based on visual clues and past experience to compensate for asymmetric loads and prevent excessive tilt of the object (Lee-Miller et al. 2019 J Neurophys 121:2276). In those experiments, the hands were placed on each side of the box. In the present study subjects lifted a visually symmetrical box by a centered handle with the right hand and also grasped the left side of the box with the left hand. Thus, depending on location of an asymmetric load, the left hand could compensate for tilt of the box as it was being lifted by pushing upward (if additional load on the left side) or downward (if additional load on the right side). We studied the role of proprioceptive feedback by having subjects first perform without vision and by randomly varying the load magnitude and symmetry (symmetric loading and asymmetric loading) so that subjects could not use anticipatory control mechanisms. For comparison, similar lifts were also made with vision allowed, but also with randomly varied load symmetry and magnitude to test whether allowing vision improved control of the lift. Subjects were instructed to lift the box in one smooth movement to a level orientation about 6 in. above the table. Nine right-handed subjects (4 females) first performed 9 lifts with symmetric loads to experience the different possible total loads (3 consecutive lifts with each of 200, 400 and 800 g loads added to the box that weighed 745 g). We assessed timing of movement onset and peak velocity of the left and right sides of the box to assess temporal coordination as well as maximum box tilt during the lift and box tilt at completion of the lift. Temporal coordination was much better when the load was distributed to the left side of the box as onset of left side motion averaged 21 ms later than right side motion in contrast to 107 ms average delay in onset of right side motion when the load was distributed to the right side of the box($p<0.05$). Variability of these onset time differences were also much lower when the load was distributed to the left side of the box ($p<0.05$). However, maximum tilt of the box during the lift was greater when the load was distributed to the left side of the box ($p<0.05$). Vision reduced duration, improved temporal coordination (timing of left and right side peak velocities closer to simultaneous) and decreased variability of maximum tilt during the lift but did not affect box tilt at movement termination. We conclude that proprioception adequately controls bimanual lifting, but adding vision improves temporal coordination and compensation for asymmetric loads when lifting boxes of unknown load and load distribution.

Disclosures: W. Darling: None. **L. Mikhail:** None. **J. Adhikari:** None.

Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.14/Z28

Topic: E.04. Voluntary Movements

Support: National Research, Development and Innovation Fund, Hungary, GINOP 2.3.2-15-2016-00022

Title: Cycling mode does not affect endpoint jerk in arm cycling

Authors: L. BOTZHEIM[1,2], M. MRAVCSIK[1,2], D. PIOVESAN[3], ***J. LACZKO**[4,1,2]; [1]Neurorehabilitation and Motor Control research group, Wigner Res. Ctr. for Physics, Budapest, Hungary; [2]Univ. of Pecs, Pecs, Hungary; [3]Biomedical, Industrial, and Systems Engin., Gannon Univ., Erie, PA; [4]Fac. of Information Technol. and Bionics, Pazmany Peter Catholic University,, Budapest, Hungary

Abstract: We investigated the smoothness of arm cycling movements which were performed on a custom-made cycling device in which the two handles (left and right) were unconnected, and the 2 arms could cycle independently. The crank length of the device was set to 10 or 15 cm. Twelve able-bodied persons (6 male, 6 female, 26.9 +/-6.4 years) performed arm cycling on this device with the short and long crank length as well. Cycling was performed bimanually either with hands cycling in phase (0-degree phase difference) or in counter-phase (180-degree phase difference). In both phase conditions with both crank lengths, the participants cycled for 30 seconds with a cadence of 60 rpm. Coordinates of markers placed on the participant's hand (end position of the limb), and on the cranks of the device were recorded with a sampling frequency of 100Hz, using an ultrasound-based motion capture system (ZEBRIS, Germany). The endpoint jerk as a function of time was computed as the third time derivative of the position of the marker on the hand. The squared jerk was then integrated for the movement time to get the total endpoint jerk. The total jerk obtained in the two-phase conditions was compared by the Friedman test. The jerk computation was performed separately for those cases when the crank length of the device was 10 and 15 cm. The statistical analysis did not show significant differences regarding the endpoint jerk obtained in the 2 cycling modes (in phase versus counter-phase). This holds for cycling with short and long crank lengths as well. We conclude that independent bimanual arm cycling movements are well controlled in terms of smoothness of the cycling even if the cycling person has to pay attention to keep the phase difference between the cranking of the left and right arms. In medical rehabilitation arm cycling is often applied using cycle ergometers with mechanically connected left and right cranks. We assume that arm cycling with devices in which the handles (cranks) are unconnected is a more challenging motor task from a control point of view and we suggest using it in medical rehabilitation, as not only the muscle strength but the ability of central motor control and of smooth movement execution may also be maintained using various arm cycling protocols. Further studies are needed to investigate the ability for smooth arm cycling of persons with neural motor impairment.

Disclosures: L. Botzheim: None. **M. Mravcsik:** None. **D. Piovesan:** None. **J. Laczko:** None.

Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.15/Web Only

Topic: E.04. Voluntary Movements

Support: R01HD092481

Title: Immediate improvements in paretic and nonparetic arm following bimanual skill practice-behavioral and neurophysiological effects

Authors: J. HESLING[1], J. JACOB[2], M. YAMADA[2], *S. KANTAK[1,3];
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Abstract: Most actions of daily living engage the two arms in spatiotemporal coordination to improve efficiency of performance. After stroke, deficits are evident in both the contralesional paretic and ipsilesional nonparetic arm; thus affecting bimanual performance. Bimanual skill practice may be used to improve bimanual performance; however, the influence of bimanual skill practice on the paretic and nonparetic arm as well as associated neurophysiologic changes remain unknown. Eleven individuals (age_m = 61.8) with mild-to-moderate impairments following a unilateral stroke (FM_{range} = 38-65; FM_m = 56.10) practiced 400 trials of a novel functional bimanual motor skill task. Performance improvements of the paretic and nonparetic arm were measured before and after motor practice. Corticospinal excitability of the ipsilesional and contralesional motor cortex between the two motor cortices were measured using transcranial magnetic stimulation before and after motor skill practice. Despite performance differences between the two arms, nonparetic arm improvements (Pre_m: 93.96+6.1 sec; $Post_m$: 74.22+5.7 sec) were comparable to the paretic arm improvements (Pre_m: 108.06+12.9 sec; $Post_m$: 87.59+12.7 sec). While contralesional motor cortical excitability demonstrated significant practice-induced increase (Pre_m: 880.2+298.7 μV; $Post_m$: 1219.2+244.4 μV); there was little effect of practice on the ipsilesional motor cortical excitability (Pre_m: 513.6+140.1 μV; $Post_m$: 516.6+110.9 μV). These results suggest that bimanual skill practice improves the performance of the paretic and nonparetic arm in individuals with stroke, and increases the contralesional corticospinal excitability. The ipsilesional motor cortical excitability is resistant to bimanual practice effects; a potential deficit that may underlie sustained performance deficits of the paretic arm.

Disclosures: J. Hesling: None. **J. Jacob:** None. **M. Yamada:** None. **S. Kantak:** None.

Poster

PSTR087. Interlimb and Bimanual Control

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.16/AA1

Topic: E.09. Motor Neurons and Muscle

Support: NIH: R21 NS111765
Emory National Primate Research Center (Office of Research Infrastructure Programs P51-OD011132)

Title: Transcranial magnetic stimulation of the primary motor cortex hand area in awake rhesus monkeys elicits bilateral motor evoked potentials in hand muscles.

Authors: *C. M. BUETEFISCH[1], T. WICHMANN[2,3,4], J. TRAN[2], D. LOCKLIN[3,4], C. M. EPSTEIN[2], Y. SMITH[2,4,3];
[1]Neurology, Rehabil. Medicine, Radiology, [2]Neurol., [3]Emory Natl. Primate Res. Ctr., [4]Udall Ctr. of Excellence for Parkinson's Dis. Res., Emory Univ., Atlanta, GA

Abstract: In humans, transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) readily elicits motor evoked potentials (MEP) in contralateral hand muscles via the fast-conducting crossed motoneuronal fibers. However, ipsilateral MEPs are difficult to evoke in the healthy mature brain but are more common after stroke. Such ipsilateral responses may be mediated via bilateral components of the primate corticospinal tract (CST). Determining the origin of these responses is important for our understanding of the plasticity of the CST in stroke and other brain disorders. We therefore studied ipsi- and contralateral motor responses to TMS in awake non-human primates. Experiments were conducted in 2 adult (4-8 years old) male rhesus monkeys. The animals were surgically prepared and trained to accept experimentation. During the TMS studies, we recorded surface electromyograms (EMG) from the extensor carpi ulnaris (ECU). TMS was performed with a 40 x 100 mm double rectangle iron-core coil excited using a cosine pulse. The coil was initially positioned over the stereotactic location of the M1 hand area and moved in 0.5 cm increments to determine the location of a TMS arm movement 'hot spot' which was subsequently used to elicit motor evoked potentials. Following 'hot spot' identification, the cortical area was injected with an anterograde AAV to map its efferent connections. Monkeys tolerated the TMS well, allowing us to record MEPs at rest. In both animals, TMS of the left or right M1 elicited MEPs in ipsi- and contralateral ECU muscles. MEP amplitudes increased with intensity of TMS. Resting motor threshold of ipsilateral MEP was higher (1.2- 1.5 times) than the contralateral MEP, and ipsilateral MEP amplitudes remained consistently smaller at maximum stimulation intensity. Unilateral M1 TMS evoked contralateral fingers, hands and arm movements as well as ipsilateral hand and arm movements at higher intensities. Latencies remained stable across all TMS intensities. The latency of contralateral MEP was about 3 ms shorter than ipsilateral MEP in animal 1 but was within 1 ms in animal 2. Postmortem analysis of AAV transport revealed patchy anterograde labeling in the contralateral M1 and profuse terminal staining in the ipsilateral and contralateral medulla and spinal cord. When compared to the results of humans, TMS elicited ipsilateral MEP at lower intensities. Consistent with the results from humans, the differences in the latencies of ipsi- and contralateral MEPs suggest that they were mediated by different connections. These data suggest that the TMS monkey model is suitable for invasive testing of proposed pathways mediating the ipsilateral response to TMS.

Disclosures: C.M. Buetefisch: None. **T. Wichmann:** None. **J. Tran:** None. **D. Locklin:** None. **C.M. Epstein:** None. **Y. Smith:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.01/AA2

Topic: E.05. Brain-Machine Interface

Support: NIH Award No. 5U01EB02760
DoD Award No. W81XWH-16-1-0722
Virginia CCF Award No. MF19-108-LS

Title: A wearable M-mode ultrasound system that can reliably control a prosthetic hand

Authors: *S. ACUNA, Z. TAGHIZADEH, M. J. JIRSARAEI, A. A. BASHATAH, S. SIKDAR;
Bioengineering, George Mason Univ., Fairfax, VA

Abstract: Sonomyography, the ultrasound-based sensing of muscle deformation, is an emerging alternative sensing modality for upper limb prosthesis control. Sonomyography enables spatiotemporal characterization of both superficial and deep muscle activity, making it possible to distinguish the contributions of a large set of muscles when deriving prosthesis control signals. We have recently incorporated a new ultrasound imaging approach that enables the miniaturization of ultrasound instrumentation using low-voltage commodity hardware and low-frequency processing speeds. We present a 4-channel wearable ultrasound system capable of tracking in vivo muscle interfaces that can feasibly be used to control a prosthetic hand. To examine the reliability of this system, we asked 10 able-bodied subjects to perform 5 different hand grasps (including rest, power, tip, point, and key). Our system uses M-mode ultrasound images to assess the motion and timing of the internal structures, which are used to derive the prosthesis control signals. We use machine learning to recognize the patterns of user intent (analogous to pattern recognition for myoelectric control). We are currently classifying ultrasound features using a Decision Tree Classifier. We found that our system could classify the 5 hand grasps with 98.5% accuracy. This study shows strong feasibility for a low-voltage wearable ultrasound system that can control a prosthetic hand. The high spatial and temporal resolution of our approach shows promise for generating reliable control signals that are intuitively executed by the user and require minimal training. In a previous study, we found that transradial amputees could achieve 96% classification accuracy for 5 unique hand grasps after only a few minutes of training the algorithm. We anticipate that our implementation of low-power ultrasound imaging will serve as the foundation for future prosthetic and exoskeleton designs. One of the primary benefits of the sonomyographic sensing modality is that muscle activity can be sensed with high spatial specificity, even in deep-seated muscle compartments. This presents opportunity to derive more independent control signals than electromyographic sensing can provide.

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property rights/patent holder, excluding diversified mutual funds); Listed on a patent using the ultrasound technology described in the abstract.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.02/AA3

Topic: E.05. Brain-Machine Interface

Support: NIH Grant P20GM103430

Title: Human-inspired vision-based reaching and grasping for assistive robotic arms with reinforcement learning

Authors: R. BEYER[1], A. RABIEE[1], S. OSTADABBAS[3], ***R. ABIRI**[2];
[1]Dept. of Electrical Engin., [2]Dept. of Biomed. Engin., Univ. of Rhode Island, Kingston, RI;
[3]Electrical & Computer Engin. Dept., Northeastern Univ., Boston, MA

Abstract: Humans have a remarkable ability to grasp and manipulate various objects effortlessly in their everyday life. Due to their experience, they know intuitively how to grasp a wide range of objects. However, individuals who experienced a stroke, spinal cord injury or multiple sclerosis leading to limited or no voluntary limb muscle control, require assistance from caregivers for activities of daily living (ADLs), such as eating and drinking tasks. Hereby, a recent study predicts a global shortage of 15 million healthcare workers in 2030. The study concludes that this shortage may not occur when labor productivity increases through the better utilization of technology. Assistive robots have the potential to significantly reduce this shortage and assist healthcare professionals in providing ADLs to these individuals. However, most of the current robotic grasping research focuses on top-down two-finger grasps for industrial robotic arms. These traditional grasps are not always helpful in the context of providing assistance to these individuals. In ADLs, where the arm needs to grasp objects upright and without obstructing their openings, as in the case of drinking from a mug, these approaches are not useful. This study and ongoing project aim to perform reaching and grasping tasks in a human-inspired manner. Using closed-loop deep reinforcement learning algorithms (DRLs) and a human-inspired setting regarding camera position, alignment of the robotic arm and type of gripper used, the goal of this work is to perform a reach and grasp task with the most natural execution possible. During the initial simulation run, the arm is able to grasp one object with success rate of 80 percent.

Disclosures: R. Beyer: None. **A. Rabiee:** None. **S. Ostadabbas:** None. **R. Abiri:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.03/AA4

Topic: E.04. Voluntary Movements

Support: CMMI 2128465

Title: How is user performance and strategy in high dimensional hand control of a robot influenced by the command variables controlled (joint positions, end effector position, joint velocities, end effector velocity, or joint torques)?

Authors: *S. E. KHAN, Z. C. DANZIGER;
Biomed. Engin., Florida Intl. Univ., Miami, FL

Abstract: The best way to give people control over complex robots (e.g., surgical robots, excavators, or mobile industrial robots) remains an open question. In this work we explore the possibility of turning a user's finger joint angles into a high-dimensional "joystick", letting us harness a fluid and rich space of user signals for robot control. However, this raises the question of what robot command variables we should link to the user's movements. Previous studies, investigating control of computer cursors, found that people's performance at cursor control tasks is substantially impacted by the command variables that they control (e.g., cursor position versus velocity). We hypothesize that the effect of command variables has an even greater impact when controlling robots due to the added dynamics. In this work, we investigate what the optimal set of command variables is for controlling a robot from a high dimensional control space. We provide 5 groups of participants control of a 6 degree of freedom (DOF) robot arm via the 19 joint angles of their fingers. Participants' finger joint angles in each group are mapped to a different set of robot command variables: joint positions, joint velocities, end effector position and orientation, end effector velocity and orientation, or joint torques. We utilize the participant's finger joint angles as the inputs because they provide a high-dimensional input signal over which a person has precise control. Additionally, the dimensionality imbalance between the participant's 19-D inputs and the 6-D command provides participants the flexibility to use many postures to achieve the same robot action. We linearly project (via subject-calibrated Principal Components) the 19-D finger joint angles to the 6-D robot command variables. Participants in all groups control the robot to perform the same task of picking up objects and placing them into target locations. Participants are evaluated in terms of the time it takes them to complete each task stage (where stages are: gripper contact with object -> object grasp -> object lift -> object place). Preliminary data from joint position and end effector position groups revealed large intra-group performance variability. This finding indicates that, regardless of selected command variables, large performance gains may be obtained by implementing individual-specific interventions during learning such as varying feedback or adapting the user-to-robot map.

Disclosures: S.E. Khan: None. **Z.C. Danziger:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.04/AA5

Topic: E.05. Brain-Machine Interface

Support: 90REMM0001

Title: Impact of actuation mechanisms on motor adaptation during assisted hand movements

Authors: *T. Q. PHAN, M. ALGHAMDI, M. L. TSCHANTRET, S. LEE;
Catholic Univ. of America, Washington, DC

Abstract: Various robotic devices have been developed for training of the hand of stroke survivors. Current assistive devices for hand training can be classified into two types based on their actuation mechanisms: end-effector (assistance delivered to the fingertip) and cable-driven exoskeleton. While the differences in their function have been well described, their differential impacts on motor adaptation at the muscle level, despite its significance in long-term recovery, remain largely unknown. The two actuation mechanisms induce distinct sensations of proprioception and joint stability, which can affect motor adaptation patterns of the users.In this pilot study, we examined the impact of assistance delivery mechanisms on the muscle coordination pattern of the hand during assisted finger movements. Four neurologically-intact subjects participated in an experiment in which they extended their index finger against resistance. Two types of robotic devices were used to assist finger extension movement: 1) end-effector device to move the fingertip to a predetermined trajectory, and 2) exotendon (cable-driven) device that provides assistance via a cable that mimics the path of the finger extensor musculotendon. Each subject performed timed finger extension movements (2-second movement: dynamic phase; 3-second hold: static phase) 10 times per condition (no assistance; end-effector; exotendon). The excursion lengths of the actuators were calibrated so that two devices produced the same range of movements. Activities of the three task-related muscles, extensor digitorum communis (EDC; agonist), flexor digitorum superficialis (FDS; antagonist), and first dorsal interosseous (FDI; synergist) were recorded. While both actuation mechanisms significantly reduce activation of all three muscles, the overall muscle activation level during the dynamic phase was lower under the exotendon assistance than the end-effector assistance (mean activation under exotendon vs. end-effector - EDC: 15% vs. 18%, FDS: 14% vs. 16%, FDI: 10% vs. 13%). The difference further increased during the static phase (EDC: 9% vs. 13%, FDS: 11% vs. 14%, FDI: 5% vs. 9%). In 3 of 4 subjects, significantly larger peak values of intermuscular coherence were observed under endpoint assistance, indicating the type of assistance could have affected the amount of common neural input to the hand muscles. The outcomes of this study suggest that the end-effector device may increase cocontraction of the hand muscles, when compared to cable-driven devices, possibly due to its greater impact on the neural coupling between the muscles.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.05/AA6

Topic: E.05. Brain-Machine Interface

Support: EFRE.NRW 0801790, GE-2-2-023

Title: An Intelligent Exoskeleton Assistance System for Neurorehabilitation

Authors: *M. METZLER[1,2], O. ALI[1], C. KLAES[1,3,2];
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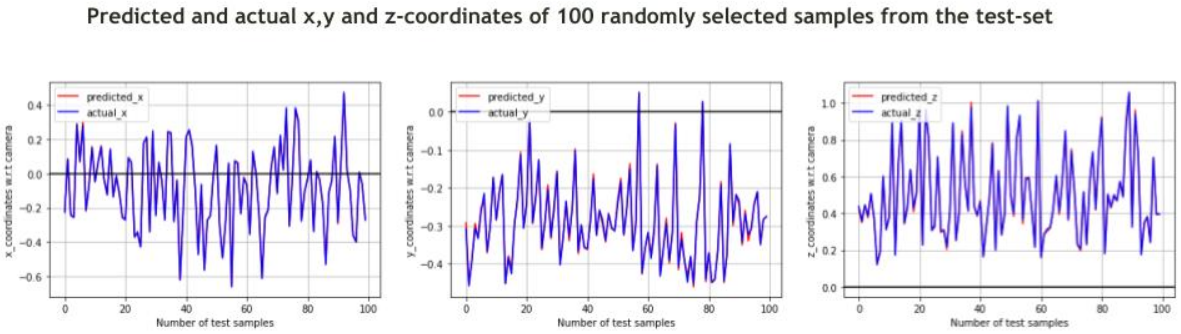
Abstract: The development of robotic exoskeletons for neurorehabilitation has moved forward tremendously during the past two decades because of their positive impact on recovery of sensorimotor functions. The driving motivation is to design them mobile, lightweight and intelligent to assist in activities of daily living. However, this is challenging because it requires accurate object and movement tracking as well as the prediction of the user's movement goal. In this study, we developed a first version of an AI assistance system that controls a human avatar in a virtual environment. The application of virtual reality allows for fast and inexpensive prototyping of assistive technologies and facilitates the creation of huge amounts of synthetic training data. Our test case is to assist in a drinking task. Thereby the assistance system provides full support in case the patient isn't able tomove its arm and hand at all or corrects the movement if the user has difficulties in finishing the movement task. To let the assistance system create appropriate control commands, it needs to know where the target objects are located. Therefore, we developed a tracking algorithm that predicts 3D object positions using input from one virtual camera that was attached to the avatar's shoulder. The algorithm consists of two modules: a detection module that tracks objects in 2D space using Yolov3 and a transformation module that maps from 2D space into 3D space. For precise and robust tracking, we generated synthetic training data with over one hundred thousand different positions of the avatar's body and hand, as well as the task objects. Detailed results for 3D position estimation for all objects are shown in Figure 1. Our VR prototype of an intelligent assistance system works well for assisting during drinking scenarios and can be trained for more movement tasks such as rotating a key to lock or unlock a door. Finally, it could be fine-tuned for controlling a real exoskeleton in future projects.



Disclosures: **M. Metzler:** None. **O. Ali:** None. **C. Klaes:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.06/AA7

Topic: E.04. Voluntary Movements

Support: NIH NINDS Grant R01NS053606
Swiss National Centre of Competence in Research (NCCR)

Title: Error Fields for personalized robotic treatment

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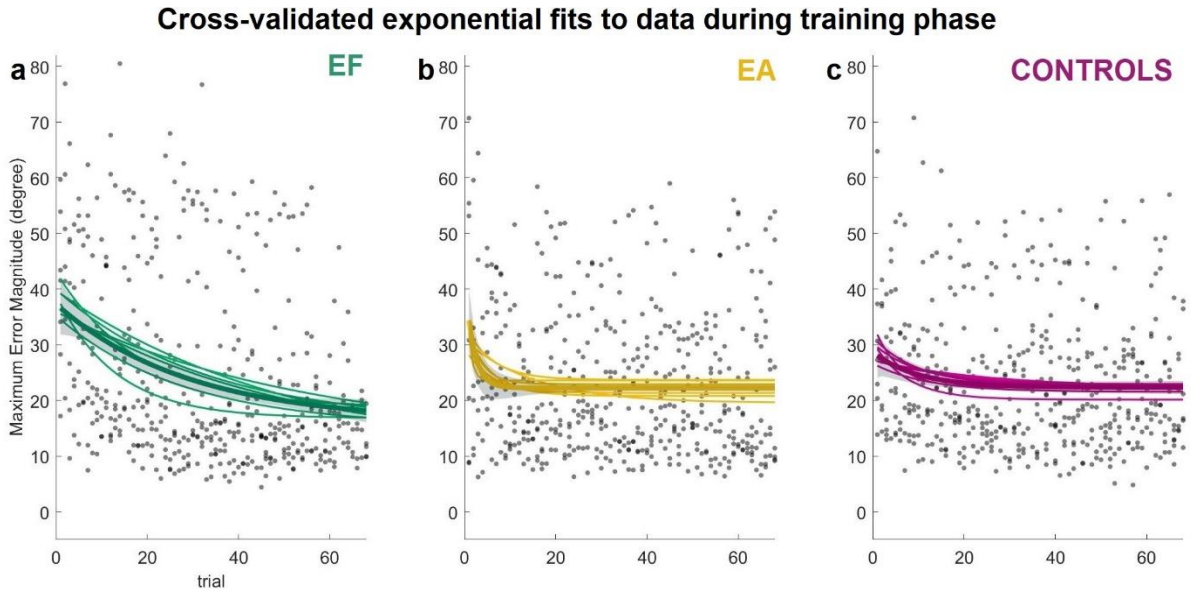
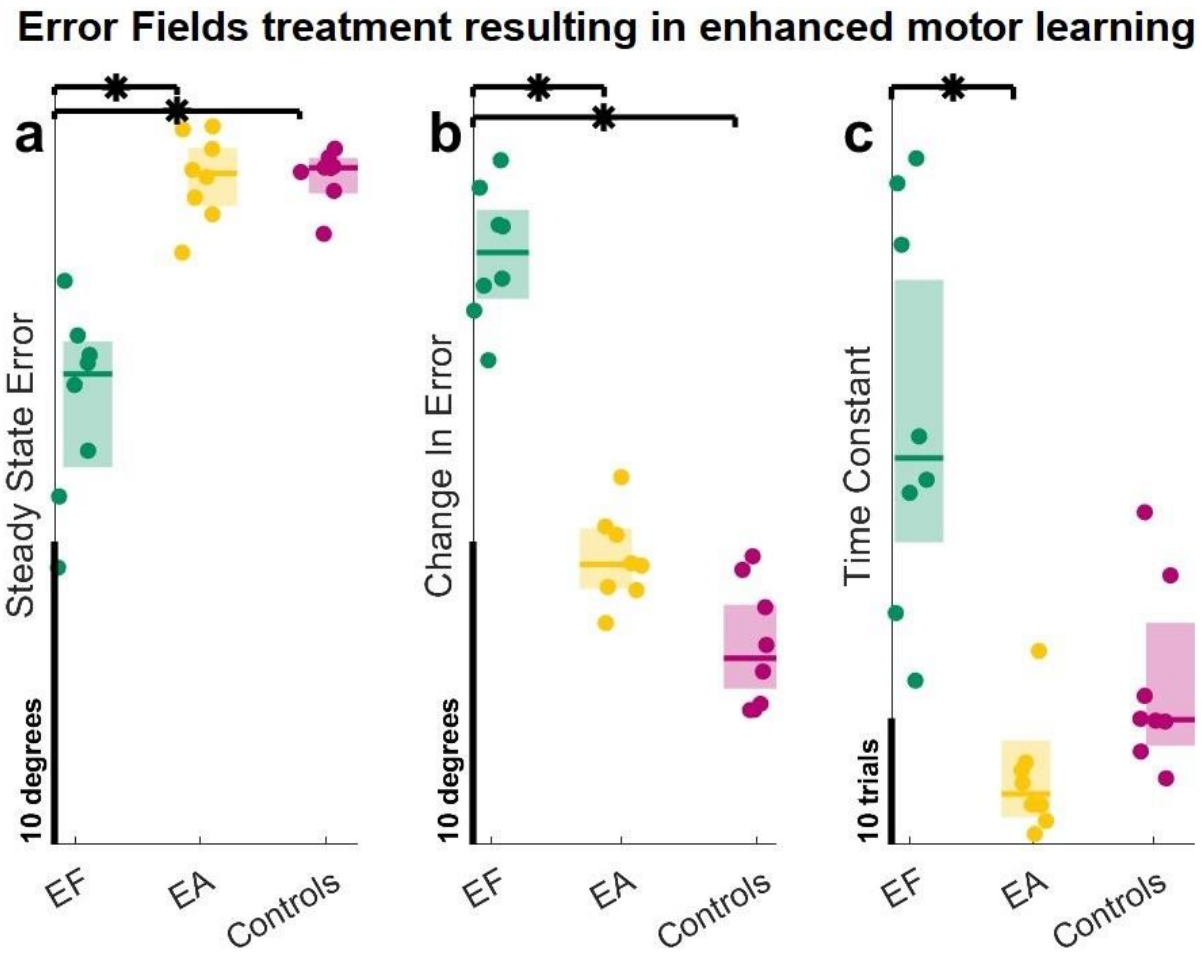
Abstract: Understanding how movement error influences learning is crucial to the understanding of neuroplasticity, prediction of learning, recovery mechanisms, and the development of treatment plans (Takiyama et al., 2015; Herzfeld et al., 2014). Studies have demonstrated that artificially amplifying haptic or visual errors through Error Augmentation (EA) (Sharp et al., 2011) can improve motor adaptation by altering the feedforward plan (Imamizu et al., 2000), thus encouraging learning that may not be otherwise achieved through assistive approaches (Liu et al., 2018). However, EA does not account for movement variations across repetitions and individuals. Our Error Fields (EF) treatment addresses this by tempering augmentation when the error has not been repeated often (Aghamohammadi et al., 2022). We

fitted and cross-validated decaying exponentials to trial-to-trial errors(fig 1(a-c)) and found that EF training reduced error magnitude (fig 2(b)) compared to those who received EA (p=0.029) and Controls (p=0.00008). Also, EF treatment resulted in participants having significantly less steady-state error(fig 2(a)) than EA (p=0.0026) and Control (p=0.0016) groups. These results demonstrate that motor learning is better enhanced using this personalized Error Fields method, consistent with other learning studies that identify the error that has been observed before (Herzfeld et al., 2014; Ballester et al., 2015). This work offers a solid foundation for models of personalized therapy.





Disclosures: **N. Aghamohammadi:** None. **M.F. Bittmann:** None. **R. Riener:** None. **V. Klamroth-Marganska:** None. **F.C. Huang:** None. **C. Celian:** None. **A. Cancrini:** None. **A. Ramirez:** None. **A. Mostofinejad:** None. **B. Borghi:** None. **J.L. Patton:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.07/AA8

Topic: E.05. Brain-Machine Interface

Support: Johns Hopkins University Discovery Grant
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Johns Hopkins Kavli Neuroscience Discovery Institute

Title: Chronic EMG recording with Vascularized Denervated Muscle Targets (VDMTs) in a Non-Human Primate: A Pilot Study

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Abstract: During a limb amputation, peripheral nerves that supply motor innervation to the limb are transected, contributing to a significant loss of function for the individual. One surgical approach to preserve the cut nerves' function is to reroute axons to a new vascularized, denervated muscle target (VDMT). Previous studies have shown that after a three month period of reinnervation, electromyography (EMG) signals from VDMTs in rodent models allow for accurate prediction of motion intent for a single degree of freedom (DOF) in the upper limb. In this exploratory study we developed a procedure to examine the effectiveness of VDMTs for long term multi-DOF prosthesis control through wireless EMG recordings from both VDMTs and naive muscles in a free-moving non-human primate (NHP) nerve injury model. To the author's knowledge, this is the first instance of multi-channel wireless recordings in a free-moving NHP. The goals of the study were to 1) achieve long-term (9 month) stable acquisition of discrete signals from implanted electrodes interfacing with VDMTs and 2) demonstrate the potential for efficacious prosthesis control utilizing the EMG recordings. All experimental procedures were approved by the Johns Hopkins Institutional Animal Care and Use Committee. Before experimentation, the NHP was trained on a simple reach and grasp task for 1-2 months. During surgery, seven cuff electrodes that each housed 4 electrode channels were placed on 4 VDMTs (VDMTs were constructed from the biceps /musculocutaneous nerve, triceps/radial nerve, flexor digitorum superficialis/median nerve, and flexor carpi ulnaris/ulnar nerve) and 3 naive muscles (extensor digitorum communis, posterior deltoid, and anterior deltoid). Following a rest period after surgery, the NHP was fitted with a custom backpack (Lomir Biomedical Inc, Canada) that housed a Brain Interchange ONE recording system (CorTec GmBH, Germany) and a Surface Go tablet (Microsoft Inc, Washington) to interface with the recording controller. Impedance measurements of the electrodes were taken on days 0, 90, and 150-158. At the 150-158 day mark, we recorded EMG signals and video data (Teledyne Flir LLC, Oregon) for animal pose estimation while the NHP performed the trained task. The study was terminated 9 months post-surgery. Our preliminary results show successful long-term EMG recordings, but lack sufficient detail to discern individual actions. Our key findings include protocol modifications for future free-moving primate experiments. Further studies which build on this pilot experiment and obtain additional recordings are necessary to reliably correlate EMG signals to limb movement.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

Support: Johns Hopkins University Discovery Grant
NSF Graduate Research Fellowship Grant No. DGE 2139757
Johns Hopkins Kavli Neuroscience Discovery Institute

Title: The effects of epimysial electrode substrates on the health of reinnervated muscle constructs

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Abstract: After amputation, muscle reinnervation surgeries have been shown to prevent the development of painful neuromas and restore motor function. After a period of regeneration, reinnervated muscle produces electromyography signals which can be used as a control source for advanced prosthetic limbs. Recording these signals for restoration of motor function requires an electrode. One type of electrode used to interface with healthy muscle tissue is an epimysial electrode, which lays on the surface of the muscle's epimysium. However, it is necessary to investigate whether epimysial electrodes are also suitable for regenerating muscle, which undergoes a significant period of atrophy before reinnervation. One rodent study reported increased atrophy when using epimysial electrodes to interface with one type of reinnervated muscle, the Regenerative Peripheral Nerve Interface (RPNI). Since the RPNI approach uses a completely devascularized muscle graft, it relies heavily on diffusion of blood and nutrients across the surface area while it is undergoing revascularization. It has been theorized that an epimysial electrode which blocks a significant proportion of the muscle's surface area may contribute to increased atrophy of the regenerating muscle. However, this has not been thoroughly tested in previous studies. Therefore, one goal of this study is to systematically investigate whether the presence of a substrate electrode causes additional atrophy in a regenerating muscle. A secondary goal is to explore the effects of an electrode on other common muscle reinnervation surgeries. More specifically, our group has developed a novel approach known as a Vascularized Denervated Muscle Target (VDMT) in which a vascular leash is kept intact, allowing for necessary nutrients to be passed from the bloodstream. In this study, 8-10 week old male Lewis rats (n=24) were equally split into 4 groups: denervated control, de-inserted/de-originated control, experimental RPNI, and experimental VDMT. Each of the 24 rats had an electrode substrate with a thickness of 20 microns and length of 6 mm implanted on one leg, and the contralateral leg was used as a direct comparison control without a substrate. After 3 months post surgery, which is sufficient time for the nerve to reinnervate the soleus muscle, we used compound muscle action potentials (CMAPs) and histological analysis to characterize the different tissue for signs of atrophy and fibrosis.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.04. Voluntary Movements

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Title: Auricular muscle for motor control in human-machine interfaces

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Abstract: Human-machine Interfaces (HMIs) have evolved over the years. They can play a key role in devices used to restore or augment motor functions. HMIs based on the recording and processing of muscle signals are quite common for their easiness of use and low cost. For this reason, identifying new sources of control to extend the applicability of this approach is very interesting. Here we explore the use of the auricular muscle (AM), a vestigial muscle in humans that has lost its original function through the evolution process, for HMIs purposes. In this study, we developed a 10 sessions training composed of biofeedback training for auricular muscle contraction and bidirectional cursor control tasks as HMI's application, which was conducted with 8 healthy subjects. Our behavioral assessment shows that through the biofeedback training, all the subjects manage to improve their muscle selectivity increasing their independent control of each muscle and reducing the residual activity in facial muscles (risorius and zygomatic muscles) to less than 5% of its maximum voluntary contraction. With the cursor control tasks, the subjects were requested to control a cursor to reach a target and we could observe a significant improvement in the success rate of 86.67 ± 10.00% and with a final distance from the target of 4.50 ± 2.10 pts in the last session, that was already significant in the fifth session. Moreover, we analyze the corticomuscular coherence (CMC) of the muscle and the neural activity over the sensorimotor cortex. Our results show increased coherence for the beta rhythm with the muscle activity, that has an expected laterality response and that it significantly differs from the fifth training session on. Previous studies have shown correlates of CMC in motor control and particularly the relevance of its change in motor rehabilitation. We also found a significant decrease in the beta desynchronization before the beginning of the motor tasks in sessions 5 and 10, suggesting less need for motor preparation for the following task. These findings show that few training sessions are enough to have neural changes due to motor

learning, which can be used to explore more the potential of such muscles for HMI application. Together, the behavioral outcomes and the neural correlates demonstrate the potential for motor learning with the AM, suggesting the possibility of recovering and repurposing the AM for interfacing with external devices.

Disclosures: D. Leal Pinheiro: None. **J. Faber:** None. **S. Micera:** None. **S. Shokur:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5R01NS105132

Title: Regenerative Peripheral Nerve Interfaces (RPNIs) and Implanted Electrodes Improve Online Control of Prostheses for Hand and Wrist

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Abstract: Prosthetic limbs and pattern recognition systems can enhance functionality for people with upper limb amputation, but suffer from low signal-to-noise ratios (SNRs) from surface electrodes and require frequent recalibration (Hargrove et al., 2017). Intramuscular recording electrodes improve control precision, reliability, and recalibration frequency (Ortiz-Catalan et al., 2020). Following amputation, there may not be sufficient residual innervated muscles available to provide complex movements of the fingers and wrist. Regenerative Peripheral Nerve Interfaces (RPNIs) surgically provide new muscle targets to the peripheral nerve and amplifies efferent nerve activity to compensate for absent muscles needed for prosthetic control (Vu et al., 2020). Here we compare the online performance of both grasp and wrist control between implanted and surface electrodes during static and dynamic arm postures. Two people with transradial amputation (P1, P2) had intramuscular bipolar electromyography (EMG) electrodes placed in their RPNIs and residual muscles. For P1, electrodes were placed in previously created RPNIs (1 median, 2 ulnar nerve) and 5 residual muscles (incl. wrist flexor). For P2, electrodes were implanted at the time of RPNI creation (2 median, 2 ulnar, and 1 radial nerve) and in 7 residual muscles (incl. wrist supinator & pronator). Percutaneous electrodes were then connected to a neural signal processor (Blackrock Neurotech) and real-time computer. Participants calibrated movement classifiers (Linear Discriminant Analysis) using a virtual hand to perform predetermined finger and wrist movements. Online control evaluated three sensing modalities separately: implanted, gelled surface, and dry surface electrodes. Classification rates represent

total accuracy for every 50 ms bin, with 60 trials and 6 classes per set for P1 and 70 trials and 7 classes for P2. Implanted electrodes outperformed gelled and dry surface electrodes, particularly during movement. P1 achieved accuracy rates of 89.4% (implanted), 84.1% (gelled), and 73.4% (dry) during static posture, while P2 achieved accuracy rates of 89.7% (implanted), 77.0% (gelled), and 60.8% (dry). During dynamic posture, P1 achieved accuracy rates of 83.0% (implanted), 60.2% (gelled), and 26.5% (dry), while P2 achieved accuracy rates of 75.4% (implanted), 55.4% (gelled), and 30.8% (dry). RPNIs and implanted EMG electrodes improved prediction of multiple grasps and wrist movements compared to gelled and dry surface electrodes. Increased stability during dynamic arm postures suggests implanted electrodes may yield more reliable control across a wide range of everyday activities.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR088.11/AA12

Topic: E.05. Brain-Machine Interface

Support: NSF Grant #1926576
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NIH Grant 1U41NS129436-01

Title: Non-human primate direct motor point fes for dexterous hand movement

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Abstract: Functional electrical stimulation (FES) enables neuroprosthetic control of functionally disconnected limbs. FES for upper extremity movement includes surface electrodes, intramuscular electrodes, intrafasicular electrodes, and nerve cuff electrodes. However, individuated hand and finger movements remain a challenge. Direct motor point stimulation is an anatomically based technique that initiates stimulation from the terminal end point of peripheral nerves. Studies have shown that motor point stimulation can produce specific muscle contraction in lower extremity (Marsolais et al 1988, Popovic et al 1991). However complete implantation, stimulation, and finger individuation has not yet been demonstrated in non-human primate (NHP) or human (Schieber et al 1991, 2001, Liu et al 1996). We demonstrate, for the first time, that access to upper extremity motor points can be safely achieved for in-vivo implantation, stimulation, and individuation of finger movement. We confirmed the presence of motor points in ex-vivo dissection of NHP upper extremity. Then, we explored direct bipolar electrode

implantation within the upper extremity of live NHP. Intraoperative stimulation parameters for muscle belly were 5 mA,10-25 microsecond pulse width, with a 32ms interpulse interval. 3 motor points were implanted in muscle bellies of flexor digitorum profundus (FDP). 5 motor points were implanted in extensor digitorum communis (EDC). 1 motor point in flexor digitorum superficialis (FDS), 2 motor points in flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), and extensor carpi radialis brevis (ECRB). Intraoperative testing was used to confirm placement. Individuated finger flexion was elicited in middle, index, and ring finger based on direct motor point stimulation of FDP. Isolated extension movements were elicited in the index finger due to specific muscle belly implantation of EDC. Combined flexion responses from FDP motor point stimulation were elicited in index/middle, and ring/pinky finger. Compound extension movements were able to be elicited from EDC motor point stimulation for all four main digits, index/middle finger. Additionally, wrist extension and flexion were elicited from motor point stimulation at ECU, ECRB, FCU, and FCR. Using surgical approaches, we have implanted electrodes for motor point stimulation and individuated finger/hand movement *in vivo*. Given the success of this technique, we believe that we can increase the electrode count and achieve dexterous hand movement. In the future, we will combine this system with a Brain-Machine-Interface (BMI)based control system, for a complete, implantable upper extremity FES.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Support: NIH R01HD088417

Title: Effects of VR headset on joint excursions during gameplay

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Abstract: Virtual reality (VR) has been used to shape motion in patients with various orthopedic and neurologic impairments for a number of years. Results from our recent Phase II clinical trial (i.e., VIGOR trial) found that our VR dodgeball game (i.e., Dodgeality) reduced pain and disability in participants with chronic low back pain. However, this game was developed for the Vive Pro headset, was tethered to a high end computer, and was not readily available for home use. To facilitate translation of this intervention for home use, we needed to port the software to the android based platform of the Oculus Quest 2 headset. This system is an affordable

standalone that does not require a separate computer to run. However, it is unknown if motor behavior observed in gameplay with the Vive is consistent with the Oculus Quest 2 headset. Virtual Dodgeball is played in virtual basketball arena, with the participant positioned at the free-throw line on one side of the court and the four virtual opponents positioned on the free-throw line on the opposite side of the court. Virtual balls are launched every 5 ± 0.3 seconds in a randomized order from each of the 4 virtual opponents. Games consist of 3 levels with 2 sets per level and 15 launched balls per set. Eight participants played one game of Dodgeality in the Vive Pro VR headset and one game in the Oculus Quest 2. The order of the VR headset used was randomized. Movement of light-reflective marker clusters attached to the head, upper arms, forearms, hands, trunk, pelvis, thighs, shanks, and feet were tracked using a 10-camera Vicon Bonita system sampled at 100 Hz. This optoelectric-based kinematic system can track the 3D coordinates of light reflective marker clusters attached to the participant with a spatial resolution of 0.1 mm. The time-series joint angle data were derived from the 3D segment coordinate data using an Euler angle sequence of (1) flexion-extension, (2) lateral bending, and (3) axial rotation using MotionMonitor software. Joint excursions were defined as the change in joint angle from initial standing posture to posture at target contact. The joint angle excursions of the knee, hip, lumbar spine, and thoracic spine during gameplay in the two headsets were compared using paired-tests. There were no significant effects of VR headset on joint excursions of the knee, hip, lumbar spine, thoracic spine (all p's >.05). Thus, the motor behavior observed in our Dodgeality game is consistent between the original tethered version (i.e., Vive) and the home version translated to a stand-alone headset (e.g., Oculus Quest 2). This provides strong evidence for this the translation of this intervention to home-based care.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

Support: NIH Award Number K01NS127936
Washington University's McDonnell Center for Systems Neuroscience Small Grants Program

Title: First steps towards a non-invasive brain-spine interface: neural correlates of lower limb movements

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Abstract: Motor rehabilitation is a crucial therapeutic tool during recovery from spinal cord injury (SCI). However, its efficacy is limited to areas with remaining sensorimotor function. This limitation can be mitigated by leveraging the temporary prosthetic effect of spinal cord stimulation (SCS), and recent studies have shown that brain-controlled SCS can further augment rehabilitation-induced recovery. The long-term goal of the project is to develop a non-invasive brain-spine interface (BSI) based on surface electroencephalography (EEG) and transcutaneous spinal cord stimulation (tSCS) to enhance and study the rehabilitation process in people with SCI. The objective of our study was to identify the neural correlates of lower limb movement in the sensorimotor cortex of unimpaired individuals and to quantify the performance of an EEG-based movement detection algorithm using a regularized linear discriminant analysis (rLDA) decoder. BCI2000 enabled synchronized recordings of a 32-channel wireless EEG headset and EMG/IMUs at 500 Hz and 1482 Hz, respectively. Initiation of leg extension was associated with an event-related desynchronization in the central-medial cortical regions at frequency bands between 20-30 Hz. Our offline decoder performance achieved a median area under the curve (AOC) of 0.8, in agreement with similar decoders in the literature. The introduction of imagery and asynchronous tasks served as positive controls to verify robustness against movement artifacts and cue-related confounds, respectively. This is a first step towards the real-time incorporation of brain-controlled tSCS based on the detection of movement intention. In the long term, this might allow the development of personalized neurorehabilitation that maximizes the recovery of individuals with SCI.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Program #/Poster #: PSTR088.14/AA15

Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5R01NS115707
NIH Training Grant 1F31NS125982

Title: Astrocytes modulate neuronal activity during intracortical microstimulation

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[2]Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical microstimulation (ICMS) is a valuable tool to study the function of the nervous system and is critical for improving the performance of brain-machine interfaces through sensory feedback. Despite its widespread use, the specific mechanisms underlying ICMS effects remain unclear, particularly regarding the involvement of glial cells, specifically astrocytes. Recent research has provided valuable insights into the significant role of

communication between astrocytes and neurons during sensory processing. However, the precise response of astrocytes to various patterns of ICMS (uniform vs bursting) and the resulting modulation of neural activity remain poorly understood. Our central hypothesis posits that astrocytes contribute to stabilizing and suppressing neural activity during ICMS. To test this hypothesis, we employed a multimodal approach using awake in vivo two-photon (2p; cellular-level) and mesoscale epifluorescence (network-level) calcium imaging in mice. We aimed to investigate the impact of blocking astrocyte calcium activity on ICMS-induced neural activity during four different temporal patterns of ICMS delivered for 30 seconds. The ICMS paradigms included two patterns characterized by uniform stimulation at frequencies of 10 Hz or 100 Hz, as well as two bursting patterns with an average frequency of 10 Hz. Calcium activity was quantified through expression of GCaMP8m in neurons or astrocytes. Additionally, we expressed a Gq-coupled HM3D DREADD in astrocytes to modulate their calcium activity. Our results indicate that the administration of compound-21 (C21; 1mg/kg) effectively reduced ICMS-induced astrocyte calcium activity, as demonstrated by reductions of 28-84% under 2p imaging and 25-66% under mesoscale imaging (n=1). Notably, when astrocyte activity was suppressed through C21 administration, we observed a slight increase in neuronal calcium activity (1-33%; n=2) under 2p imaging and a substantial increase in neuronal calcium activity under mesoscale imaging (22-78%; n=2). The results of this study indicate that suppressing astrocyte activity during ICMS leads to an augmentation of ICMS-induced neural activity, suggesting that astrocytes play a role in suppressing neural activity during ICMS. Overall, this study provides valuable insights into the involvement of astrocytes in modulating neural activity during ICMS, contributing to our understanding of the intricate interactions between neurons and glial cells in the context of ICMS. Moreover, these findings have the potential to inform the development of more effective strategies for sensory restoration through stimulation.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR 5I01RX002654

Title: Input/output properties of FES reaching and grasping for control by a brain machine interface

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Cleveland Dept. of Veterans Affairs Med. Center, FES Ctr. of Excellence, Rehab. R&D Service, Cleveland, OH; [4]Neurol., Univ. Hosp. Cleveland Med. Ctr., Cleveland, OH

Abstract: The Reconnecting the Arm and Hand to the Brain (ReHAB) clinical trial combines a brain-machine interface (BMI), consisting of intracortical recording electrodes in motor-related areas of the brain, and a functional electrical stimulation (FES) system, consisting of nerve cuff stimulating electrodes capable of reanimating the user's paralyzed limb, with the aim to restore volitional motor function to people with high cervical spinal cord injury. Traditionally, BMIs are used to control virtual systems, robotic prostheses, and other end-effectors that have consistent mappings of inputs to outputs. Control of the user's own arm, however, introduces novel challenges related to the uncharacterized dynamics of the biological system and its interface with the stimulating electrodes, resulting in high variability between the expected and actual kinematic behavior of the arm.

Kinematic recruitment curves (RC) were acquired to quantify the effect various FES stimulation parameters have on the resolution and uniformity of the resulting joint angle mapping across each joint's range of motion. Pulse widths (PW) were randomly sampled with replacement between the threshold of activation and the max comfortable stimulation level. Joint angles were recorded at each PW once the joints were at equilibrium. This process was repeated for different muscles, combinations of muscles, and pulse amplitudes.

Surprisingly, we found that increased pulse amplitude, while corresponding to an increase in RC steepness, did not correspond to a decrease in resolution of the joint angle mapping, as determined by finding the maximum number of separable regions in the RC (Tukey's, $p < 0.05$). Similarly, incorporating co-contraction of the biceps and triceps, which we expected to reduce variance in the RC by increasing stiffness of the elbow joint, showed no increase in resolution compared to an FES pattern that did not overlap bicep and triceps stimulation. We did, however, see a large effect of day-to-day variability in joint angle mapping and its impact on BMI controllability of the arm and hand. The performance of our participant in a two degree-of-freedom, joint-position matching task increased from a 16% target acquisition rate to a 47% acquisition rate after updating the RCs.

Overall, these results indicate that changes in pulse amplitude and incorporation of co-contraction into the FES stimulation parameters do not have a large effect on the resolution and uniformity of the joint angle mapping created by an FES upper extremity system. It is likely that a method of real time feedback control would be necessary to successfully map cortical signals to motor control at a high resolution.

Disclosures: B. Alexander: None. **J. Krall:** None. **A. Ketting-Olivier:** None. **W.D. Memberg:** None. **J.P. Miller:** None. **R.F. Kirsch:** None. **A.B. Ajiboye:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.16/AA17

Topic: E.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR 5I01RX002654

Title: Functional connectivity dynamics within the grasp network during control of a brain-machine interface by a human with chronic tetraplegia

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Abstract: Motor impairment following chronic tetraplegia results in the loss of skilled grasping, which undermines a person's ability to perform activities of daily living necessary for independence. Brain-Machine Interfaces (BMIs) for restoring hand function have had limited success due to our current limited understanding of the cortical mechanisms underlying grasping in humans. Using lesion and intracortical studies, Non-Human Primate (NHP) research has shown that the visuomotor grasp network (comprised of the Anterior Intraparietal Area, the Inferior Fontal Gyrus, and the hand area of the Primary Motor Cortex) is the primary cortical circuitry that subserves the planning and execution of a wide variety of hand-object interactions and, thus, contains rich grasp-related information that could potentially be leveraged to improve dexterous grasp decoding in humans. Presently, however, very little is known about the visuomotor grasp network in humans, including its internal connectivity and how it could potentially be leveraged by therapeutic BMIs for better outcomes. In this study, we implanted a 29-year-old male (C3/C4 level AIS B Spinal Cord Injury) with intracortical microelectrode arrays in all areas of this network to investigate task-driven functional connectivity dynamics. Using a framework that combines multivariate decomposition with Granger-Causal Connectivity Analysis, we explored temporal changes in functional connectivity within the grasp network during closed-loop BMI control of a variety of grasps. Our results quantitatively demonstrate task-driven feedforward functional connectivity modulation within the grasp network for the first time in a human. In addition, we observed changes in feedback connectivity, conditioned on virtual movement onset as well as the presentation of a visual movement cue. Our findings are consistent with NHP studies suggesting sequential processing within the grasp network, but also present novel quantitative evidence of feedback interactions. By untangling the mechanisms of functional connectivity modulation within the human grasp network, we hope to open avenues for its utility in the development of more efficacious therapeutic interventions to restore independence to persons with paralysis.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Program #/Poster #: PSTR088.17/AA18

Topic: E.05. Brain-Machine Interface

Support: NSF CISE HCC award 2133879

Title: Assessing hand grasp representations in children with congenital upper limb deficiencies

Authors: *E. WINSLOW[1], M. A. BATTRAW[2], J. FITZGERALD[3], W. M. JOINER[3], M. JAMES[4], A. M. BAGLEY[4], J. S. SCHOFIELD[2];
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Abstract: Predicting motor intent using surface electromyography (sEMG) for upper limb prosthetic control requires users to exhibit unique patterns of muscle excitation. Studies in this area have been primarily focused on the adult population, especially those with traumatic amputation. However, most pediatric prosthetic users have congenital limb deficiencies as opposed to acquired limb loss, and their muscles will have never actuated a fully formed hand. It is currently unknown to what extent traditional adult amputee-based sEMG techniques will translate effectively to this population. Yet dexterous prosthetic hands have begun to emerge for pediatric users with little evidence to support their abilities to control the newly available dexterity. Together, these factors present a significant barrier to effectively translating these devices to pediatric populations. To address this gap in knowledge, we collected sEMG data from 9 participants with unilateral congenital below elbow deficiency (ages 8-20 years) as they attempted to perform a set of 11 hand grasp movements (including the rest state) with their missing limb. A Delsys Trigno Research System was used to capture the naturally occurring electrical activity of the children’s forearm muscles with 4 to 7 sEMG electrodes adhered around both the participant's affected and typical limb. Using conventional root mean squared and mean frequency characteristics, we analyzed the sEMG data, finding that each time a participant attempted to move their missing limb to a specified hand grasp, the sEMG characteristics demonstrated unique and coordinated patterns of muscle excitation. We also showed that to varying degree, these patterns were consistent across repetitions of the same attempted grasping movements. The work presented here begins to address the extent to which children born with upper limb deficiencies can actuate their affected muscles when attempting to perform specific grasping movements with their missing hand.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR088.18/AA19

Topic: E.05. Brain-Machine Interface

Support: T32EB004314

Title: Representation of grasp parameters in the inferior frontal gyrus in a human tetraplegic participant

Authors: *E. CONLAN[1,2], A. B. AJIBOYE[3], W. D. MEMBERG[3], A. KETTING-OLIVIER[3], E. L. GRACZYK[3], R. KIRSCH[3], J. MILLER[4];
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Abstract: The objective of this study is to determine how the Inferior Frontal Gyrus (IFG) modulates to grasp and object in a human participant with chronic tetraplegia. Persons with tetraplegia indicate that one of the top priorities is restored hand function, for which object interaction is the main goal. Restoration of hand grasp and object interaction would improve quality of life and allow participants to preform activities of daily living such as eating, drinking, and self-care. Brain Machine Interfaces (BMI) offer an opportunity to record signals related to grasp and object from the brain during motor visualization tasks. These signals predominantly reside in the human homologue of the non-human primate grasp network, comprised of the anterior intraparietal area (AIP), the inferior frontal gyrus (IFG) and primary motor cortex (M1). Study participant RP1 (motor complete, C3/C4 AIS B SCI), participant was enrolled into the Reconnecting the Hand and Arm to Brain (ReHAB) Clinical Trial and implanted with six, 64 channel microelectrode arrays (one in AIP, one in IFG, and two in M1, and two in primary sensory cortex). Cortical information from each area was recorded while the participant attempted forming randomized grasp-object pairs presented in a motor imagery visualization. A one-way ANOVA revealed that 58 out of the 64 recorded channels showed significant modulation when compared to baseline screen blanking activity ($p<0.05$). A subsequent two-way ANOVA with post-hoc multiple comparisons revealed that of the 58 channels, 21 tuned to grasp, 4 tuned to object, and 3 tuned to the interaction between grasp and object. In addition to determining modulation to grasp and object, and additional objective of this study was to determine the extent of modulation in different epochs of movement. Each trial was comprised of three epochs, a screen blanking period (1.5s) a premovement epoch (1.5-2s), and movement epoch (4-4.5s). Population level analysis was preformed using Linear Discriminant Analysis (LDA) on the channels tuned to grasp. Cross validated decoding accuracy for decoding grasp was determined to be 79.5±6.5% in the premovement epoch and 48.5±8.7% during the movement epoch. LDA on channels tuned to object showed a cross validated decoding accuracy of 31.0±7.1% in the premovement epoch and 30.5±5.3% in the movement epoch for decoding object. These results indicate that grasp type is the main factor contributing to modulation in IFG with strong differentiability within the premovement epoch. Future work will focus on decoding grasp state from IFG for real time grasp control in a BMI-Functional Electrical Stimulation (FES) system.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

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DoD CDMRP SCIRP grant SC180308
VAMR 5I01RX002654

Title: Decoding limb stiffness and rhythmic movements from novel cortical implant sites in a paralyzed human

Authors: *C. HADDIX[1,2], T. JOHNSON[2,1,4], A. KETTING-OLIVIER[2,4], W. D. MEMBERG[2,4], J. MILLER[3,5,4], R. F. KIRSCH[2,4,3], A. B. AJIBOYE[2,4,3], D. TAYLOR[1,4,2];
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Abstract: Restoration of practical upper limb function after spinal cord injury is now ‘within reach’ by using an intracortical brain-computer interface (BCI) to extract one’s intended movement and a functional electrical stimulation (FES) system to reanimate the paralyzed muscles. However, much work is needed to make these systems work optimally. In everyday movements, we continuously modify the amount we co-contract our antagonist muscles based on the task's requirements for stability and the likelihood of external disturbances from the environment. For example, we take more care to stabilize our arm when transporting a hot cup of coffee to our lips than when placing the empty cup back on the table. Prior human intracortical BCI studies have primarily been concerned with decoding *kinematic* movement characteristics in Cartesian or joint space for controlling computer cursors, robotic arms, and upper limb FES systems. Even though BCIs have succeeded in making useful reaching movements possible, the need to adjust limb stiffness by increasing or decreasing co-contraction of antagonist muscles has not yet been directly addressed by these efforts. We hypothesized that limb stiffness can be decoded as an independent variable after paralysis for use in FES system control. Additionally, decoding attempted or imagined movements in someone who is fully paralyzed can be challenging due to fluctuating attention and no reliable way to know the precise timing of the movements the user is attempting to make during BCI calibration. We hypothesized that playing a rhythmic beat during attempted movements as part of the decoder building process will result in more reliable movement-related neural modulation and improved BCI decoding. We tested these hypotheses in a participant with a C4 motor-complete spinal cord injury (AISA B) enrolled in the Reconnecting the Hand and Arm to the Brain (ReHAB) Pilot Clinical Trial. Neural data were recorded from intracortical microelectrode arrays across the sensorimotor network including in primary motor and sensory cortices, ventral premotor cortex (inferior frontal gyrus), and anterior intraparietal sulcus. Preliminary results suggest some stiffness decoding is possible although it is not as strong as kinematic decoding. Additionally, attempted movement of a wide

range of body parts (ankle, hip, waist, shoulder, elbow, wrist, fingers and tongue) could be classified from the ventral premotor array alone even without rhythmic timing cues.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Program #/Poster #: PSTR088.20/AA21

Topic: E.05. Brain-Machine Interface

Support: R01NS119160
R21NS128685
Cleveland Clinic

Title: Decoding muscle activity from PMd, M1 and the M1-3a border for improved control of limb stiffness in brain-controlled neuroprosthetics

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Abstract: Brain-controlled Functional Electrical Stimulation (FES) of the arm holds potential for enhancing the quality of life for individuals with paralysis. Our previous research has demonstrated that incorporating *automatic* modulation of limb stiffness, which involves varying the cocontraction of antagonist muscles, can significantly improve the precision and energy efficiency of FES-controlled reaching movements. However, *volitional* control of stiffness is also needed to enhance functionality and proactively counter anticipated disturbances. Brain-Computer Interfaces (BCI) are predominantly used to decode position and velocity. However, in our study, we extended this approach by directly decoding muscle activity and cocontraction from intracortical arrays to acquire a volitional limb stiffness command. In the initial phase of our non-human primate study, we recorded upper limb EMGs along with intracortical spiking activity from the PMd, M1, and the M1-3a border deep in the central sulcus. Rhesus macaques performed a simple motor task designed to isolate independent activation of the biceps and triceps muscles from cocontraction. Our cross-validated results demonstrated a reliable distinction between different EMG states, with the M1-3a border area exhibiting the highest number of units with strong cocontraction encoding. These EMG-state-specific responses were also observed within the framework of rotational dynamics. We subsequently trained the subjects to utilize their neural signals for real-time control of both kinematic commands (e.g., X/Y velocity) and an independent limb stiffness dimension. After familiarizing themselves with

controlling the movement of a cursor and adjusting its "stiffness" (conveyed as the cursor's resistance to an applied external oscillation), the animals' signals were employed to control a virtual upper-limb FES system in real time. This system encompassed a realistic computational model of a human arm, which continuously interpreted muscle stimulation values and determined the corresponding arm movement. We evaluated volitional stiffness modulation during movement by assessing the animals' ability to counteract external perturbations on the arm model by increasing cocontraction when necessary. Additionally, we are incorporating a robotic limb equipped with artificial muscles into our BCI-based volitional movement and stiffness control experiments. This integration aims to extend the functionality of stiffness control to robotics, in addition to its application in upper limb FES systems.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR088.21/AA22

Topic: E.05. Brain-Machine Interface

Title: Comparison of body control strategies for hand neuroprostheses in patients with tetraplegia using virtual reality

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Abstract: Hand neuroprostheses offer promise for restoring hand functions in people with paralysis due to neurological diseases such as spinal cord injury and stroke. Among hand neuroprostheses, those based on electrodes implanted in muscles [Kilgore, 2008, JHS] or peripheral nerves [Badi, 2021, Sci. Transl. Med.] offer greater dexterity compared with non-invasive technologies [Snoek, 2000, Spinal Cord]: they allow restoring a greater number of functions and grading force by modulating the amplitude or frequency of the electrical stimuli. To let patients voluntarily control hand neuroprostheses, control via residual body movements is currently the most used approach because it is robust and easy to implement [Losanno, 2023, Nat. Rev. Bioeng.]. In the case of severe motor impairment, only non-homologous movements can be exploited. The limitations of non-homologous body control lie mainly in its low intuitiveness and the fact that it can interfere with tasks involving the same body part. Here, we studied learning of two non-homologous body control strategies for hand neuroprostheses in five patients with C6 tetraplegia. We simulated neuroprosthesis use by implementing an immersive virtual reality environment in which users control the hand of a human avatar with a binary command, used to switch between grasps, and a proportional command, used to modulate grasp

closure, while their arm position is tracked and virtually replicated. We implemented the binary command using button presses and compared ipsilateral wrist extension and contralateral shoulder elevation as proportional control sources. These two strategies were chosen because they are used in commercial neuroprostheses and belong to the intrinsic and extrinsic motor task null space [Dominijanni, 2021, Nat. Mach. Intell.], respectively. Patients used these two strategies to perform unimanual and bimanual tasks mimicking activities of daily living over five consecutive experimental sessions. Longitudinally, we quantified precision, speed, and coordination and we evaluated the perceived mental and physical effort through questionnaires. Patients improved their performance significantly over time, and control became more intuitive and less physically demanding for them. The most easy-to-learn and eventually preferred and most effective strategy depended on the patient's clinical picture. Overall, the ipsilateral wrist was more effective in bimanual tasks, whereas the contralateral shoulder provided higher precision in unimanual tasks. These results offer insights into the development of effective control schemes for hand neuroprostheses that may promote their clinical acceptance.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

Support: Fitzgerald Translational Neuroscience Fund

Title: Integrating phase amplitude coupling analysis into Brain Computer Interface (BCI) algorithms to enhance motor control restoration in stroke-induced paralysis

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Abstract: Stroke is one of the major causes of disability in the world. In the United States, about 800,000 people suffer from stroke every year, with approximately half of them experiencing lifelong paralysis or paresis of one of their arms. Brain computer interfaces (BCIs) can be a solution to restore some functions in the impaired limb. The first Cortimo (NCT03913286) proof-of-concept clinical trial successfully demonstrated that activity from neurons in the primary motor cortex above a chronic subcortical stroke region can be used for restoring upper extremity motor control in the paretic limb using BCI combined with a powered orthosis. Namely, in an N-of-1 trial, four 8x8 microelectrode arrays were implanted in the ipsilesional primary motor cortex. The recorded neural activity was decoded in real-time to operate the upper extremity orthosis voluntarily. The data revealed patterns that are not commonly observed in healthy brains (non-human primate and human). The stroke-affected brain regions were found to

generate irregular signals, such as periodic cross-channel bursts, decreased gamma power and elevated delta power that were not reported in any other intracortical BCI trial that enroll people with conditions such as spinal cord injury, ALS and stroke confined to the brainstem. Investigating offline data can reveal additional neural features that capture the unique characteristics of a stroke-affected brain, informing the design of effective decoders for future trials. We propose the incorporation of real-time calculation of phase amplitude coupling (PAC) of the neural signals as a gating technique along with power spectral density (PSD) and spike firing count features which were used in the first trial. Our goal is to use PAC in real time to modify the weights of other neural features at certain frequencies to improve BCI decoding performance. We calculated PAC using modulation index to quantify the coupling between local field potential (LFP) phases in 1-4 Hz and amplitudes in the 100-500 Hz bands. This neural feature set will be utilized with linear and Kalman filters to evaluate the system's performance using the upper extremity kinematic trajectories collected during the BCI sessions. The initial results with a Kalman filter show that the PSD gated with PAC increases the similarity metric, Pearson's correlation coefficient, between the original and predicted kinematics by 7.32% compared to only PSD features. Future work will include selectively using relevant features from the incoming neural data to improve accuracy, reliability, and usability in a real-time BCI decoder.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Topic: E.05. Brain-Machine Interface

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Title: Cerebral Palsy stakeholders' perspectives on Brain-Computer Interfaces for communication

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Abstract: Brain-Computer Interfaces (BCIs) use neural signals to control a computer, and are of interest as a communication tool for people with paralysis and communication problems (communication BCI; cBCI). Whereas the majority of cBCI research focuses on adults, the

technology may also benefit children and adolescents with Cerebral Palsy (CP) with communication impairments. We aim to create a solid basis for the user centered design of cBCIs for young people with CP by investigating the perspectives on communication and cBCIs of this group, their parents/caretakers and care professionals. We conducted a survey study on 1) current communication problems and usability of currently used aids, and 2) perspectives on cBCIs. Animation videos were used to explain the concepts of cBCIs, cBCI control strategies (P300 and sensorimotor rhythms), and neural signal recording approaches (non-implanted and implanted). We report on the findings of parents/caretakers (n=17; 94% female, 48±6 years old; reporting on their child with CP GMFCS IV/V, 15±6 years old) and care professionals n=36; 94% female, 44±11 years old; reporting on their care recipients with CP GMFCS IV/V). Both groups indicated that, of a list of 12 potentially communication-limiting factors, motor impairment occurred the most frequently and was the most communication-limiting. The currently used communication aids included mainly no-tech aids (i.e., letter card; used by care recipients of n=34/36 care professionals and by children of 14/17 parents/caregivers) and high-tech aids (i.e., dynamic systems; reported by n=34/36 care professionals and 12/17 parents/caregivers). Low-tech aids (i.e., systems with static displays) were less frequently used (reported by 25/36 care professionals and 3/17 parents). Satisfaction (five-point Likert scale) with no-tech and low-tech systems was close to 'neutral' (no-tech: 2.9±0.8 and 2.9±0.9 for care professionals and parents/caregivers, respectively; low-tech: 3.1±0.9 and 3.0±1.0 respectively) and close to 'satisfied' for high-tech technologies (3.7±0.7 and 3.7±1.1, respectively). Yet, 89% of care professionals and 88% of parents reported an interest in cBCIs for young people with CP. Neither of the groups considered one of the BCI control strategies or neural signal recording approaches more suitable than the other (paired T-TESTS, $p>0.05$ for all comparisons). These results indicate that cBCIs may be of relevance for a subpopulation of young people of CP, and that in the development of the technology, P300, sensorimotor rhythms, as well as implanted and non-implanted approaches, deserve attention.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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NINDS/NIH Award #UF1NS115817

Title: Compression or noise reduction: the role of dimensionality reduction methods in understanding the brain-muscle relationship

Authors: L. H. CUBILLOS[1], ***M. KELBERMAN**[1], M. J. MENDER[2], S. NASON-TOMASZEWSKI[6], M. WILLSEY[7], N. G. KUMAR[3], T. A. KUNG[3], P. G. PATIL[4], C. A. CHESTEK[2], C. KRISHNAN[5];
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Abstract: Understanding how the brain controls muscles can be key for Spinal Cord Injury (SCI) patients, as it could inform technologies aimed at artificially recreating their disrupted neuro-muscular pathways. Dimensionality reduction techniques are commonly used to study these pathways, but it is unclear whether they extract the latent control signals (denoising) or just compress the data effectively. In this study, we investigated the results of applying several of these techniques to neural and muscle data and tested the compression versus noise-reduction hypothesis. A rhesus macaque was implanted with Utah arrays in the hand area of the primary motor cortex and seven bipolar intramuscular electromyography (EMG) electrodes, targeting muscles used for finger and wrist movement, contralateral to the array. The NHP was trained to perform a 2D finger task while intracortical activity and EMG were recorded. Three dimensionality reduction methods—PCA, NMF, and dPCA—were applied to the neural data, while NMF and PCA were applied to the EMG data. To test our hypothesis, we trained four linear decoders: one mapping from neural activity directly to EMG (NtoEMG), another from neural activity to muscle synergies (NtoSyn: 1, 3, and 5 muscle synergies), a third from neural synergies to EMG (SyntoEMG: 5, 15, and 30 brain synergies), and the final one from neural to muscle synergies (SyntoSyn; all combinations).Our results show that neural activity can predict EMG accurately (NtoEMG: R^2=0.54; avg. across muscles), and that none of the other three linear decoders can do better, regardless of the number of dimensions used for neural (SyntoEMG: 5 syn. [R^2=0.40], 30 syn. [R^2=0.52], average across methods) or EMG (NtoSyn: 1 syn. [R^2=0.39], 5 syn. [R^2=0.54], average across methods; SyntoSyn: 5 brain syn. to 1 muscle syn. [R^2=0.33] 30 brain syn. to 5 muscle syn. [R^2=0.52]). Additionally, dPCA outperformed NMF and PCA when reducing the dimensionality of the neural data, achieving better predictions regardless of the number of dimensions used. These results suggest that, with any of these methods, extracting synergies serves as a way of compressing the data effectively but not denoising it to extract a latent signal that better represents how the brain controls muscles. Additionally, the better performance of dPCA over NMF and PCA at decoding EMG with fewer neural dimensions makes it an attractive pre-processing tool for decoding algorithms by lowering the dimensionality of the data without losing decoding performance. These analyses will be repeated across multiple days and multiple contexts (varying wrist position and spring resistance), and the results will be presented at the conference.

Disclosures: L.H. Cubillos: None. **M. Kelberman:** None. **M.J. Mender:** None. **S. Nason-Tomaszewski:** None. **M. Willsey:** None. **N.G. Kumar:** None. **T.A. Kung:** None. **P.G. Patil:** None. **C.A. Chestek:** None. **C. Krishnan:** None.

Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.25/AA26

Topic: E.05. Brain-Machine Interface

Support: NSF CISE HCC award 2133879

Title: Evaluation of machine learning techniques to decode motor intent in children with congenital upper limb deficiency

Authors: *M. A. BATTRAW[1], E. WINSLOW[2], J. FITZGERALD[3], W. M. JOINER[3], M. A. JAMES[4], A. M. BAGLEY[4], J. S. SCHOFIELD[1];
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Abstract: Children's dexterous upper limb (UL) prostheses have begun to emerge that more closely resemble the form and function of intact limbs. However, control systems to operate this newly available dexterity remain predominantly based on techniques developed for adults. These often include the use of surface electromyography (sEMG) to measure the natural electrical activity of affected muscles in the residual limb as individuals attempt various missing-hand grasp motions. Machine learning algorithms are then trained to recognize the unique patterns of muscle activation and actuate the corresponding motion in the prosthesis. However, since these techniques have been primarily focused on adults with traumatic amputation, it is unknown how they may be best applied to pediatric prosthesis wearers. This is particularly relevant as most children that use prostheses were born with their limb deficiency and will have never actuated a fully formed hand. Thus, measuring their affected muscle activity for prosthetic control can present unique challenges that are distinct from adults. To begin addressing this knowledge gap, sEMG data were collected from 10 participants with unilateral congenital below elbow deficiency (8-20 years old) as they attempted to perform a set of 11 hand grasp motions with their missing limb. We then explored the offline classification accuracy of 5 common machine learning algorithms and subsets of 49 features in the time domain, frequency domain, and time-frequency domain. Data were post-processed, features were extracted, and reduction techniques were applied to find an optimal subset of 5 features for each classification algorithm that maximized accuracy. Unlike the generalized feature subsets suggested from adult literature, we found that although there were some common individual features among pediatric participants, each participant had a distinct subset that maximized classification accuracy. This work begins to address the challenges of applying and tuning machine learning techniques for dexterous pediatric UL prostheses and suggests that unlike adults, control systems for pediatric users may have to be tuned for each individual patient to maximize their efficacy.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.26/AA27

Topic: E.05. Brain-Machine Interface

Support: DOE Grant DE-SC0022150

Title: A network-inspired method to quantify sensory mapping stability for neuroprosthesis

Authors: *K. DING[1], M. M. ISKAROUS[1], L. E. OSBORN[3], M. S. FIFER[3], B. P. CHRISTIE[3], P. A. CELNIK[4], F. TENORE[3], N. V. THAKOR[1,2];
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Abstract: One key objective of developing sensory neuroprostheses is to provide reliable, long-term somatosensory feedback to individuals with sensorimotor disorders. From transcutaneous stimulation at the periphery to intracortical microstimulation (ICMS) at the somatosensory cortex, studies have shown that these electrical interfaces elicit tactile sensations in the hand. Furthermore, a growing number of studies suggest that projected fields (i.e., the locations of perceived sensation) are relatively consistent over time. However, there is thus far no consensus approach to quantify the stability of these projected fields. To address this need, we designed an approach to quantify sensory map stability by modeling projected fields as a network. We developed a stability metric that combined projected field activation frequency and co-activation with other projected fields.

We test our method with two datasets that use different stimulation techniques to generate the sensory maps. The first was a targeted transcutaneous electrical nerve stimulation dataset. Stimulation was delivered to the residual limb of a participant with trans-humeral amputation. Sensory maps were collected over 12 sessions across 5 years. Our results indicate that phantom hand regions consistently activated throughout all sessions show a high stability score. Our method properly distinguishes (through a higher score) between low activation frequency regions that are co-activated versus those that are not.

The second was an ICMS dataset. The participant had a cervical-level spinal cord injury and was implanted with microelectrode arrays in his bilateral motor and somatosensory cortices. There were 96 electrodes across the left and right somatosensory cortices. ICMS was delivered through a single electrode at a time. Evoked sensations were mapped over 52 sessions across nearly 2 years.

Overall, this work presents evidence that our network approach captures the co-activation of sensory projected fields. Our approach can be applied to sensory maps, regardless of the stimulation method, to understand how projected fields change over time. This information is important as it shows the hand regions that most consistently perceive stimulation-evoked sensations, which can guide stimulation design for reliable sensory feedback.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

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Support: NSF Grant 1926576
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Title: Balancing memorization and generalization in RNNs for high performance brain-machine interfaces

Authors: *J. COSTELLO, H. TEMMAR, M. MENDER, L. CUBILLOS, D. WALLACE, M. WILLSEY, P. PATIL, C. CHESTEK;
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Abstract: Intracortical brain-machine interfaces (BMIs) can restore motor function to people with paralysis but are currently limited by the accuracy of real-time decoding algorithms. Recurrent neural networks (RNNs) using modern training techniques have shown promise in accurately predicting movements from neural signals but have yet to be rigorously evaluated against other decoding algorithms in a closed-loop setting. Here we tested RNN decoders against other neural network architectures in a real-time BMI controlled by a non-human primate. One rhesus macaque was implanted with Utah arrays in motor cortex and trained to perform a target-acquisition task requiring simultaneous movements of one or two finger groups. Spiking-band power was recorded from each channel, averaged into bins, and fed into a decoder to predict finger velocity and position. After initial hand-control trials, we trained and evaluated five decoders in online trials: two RNN architectures (LSTM and GRU), two feedforward neural networks, and a linear Kalman filter.
Across one and two finger online tasks, LSTMs outperformed convolutional and transformer-based neural networks, averaging 18% higher throughput than the convolution network across three comparison days. On simplified tasks with a reduced movement set, RNN decoders were allowed to memorize movement patterns and matched able-bodied control for up to four target postures. Performance gradually dropped as the number of distinct movements increased but did not fall below fully continuous decoder performance. Simulated datasets suggest that increasing task complexity requires more training data or input channels to maintain decode accuracy. Finally, in a two-finger task where one degree-of-freedom had poor input signals, we recovered functional control using RNNs trained on a reduced movement set for the finger with poor input signals, which allowed the RNN to act both like a movement classifier and continuous decoder.

Our results suggest that RNNs can enable functional real-time BMI control by learning and generating accurate movement patterns. Further work may explore modifying internal decoder dynamics to accurately produce stereotyped movements.

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Poster

PSTR088. Using Neuroprosthetics to Restore Skilled Behaviors

Location: WCC Halls A-C

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Topic: E.05. Brain-Machine Interface

Support: Agencia Nacional de Investigacion y Desarrollo de Chile
NSF Award # 180405
NSF Fellowship

Title: A deep-learning-augmented Kalman filter for high-performance intracortical decoding

Authors: *L. H. CUBILLOS[1], G. REVACH[3], J. T. COSTELLO[1], H. TEMMAR[2], M. J. MENDER[4], X. NI[3], M. M. KELBERMAN[1], D. M. WALLACE[2], M. S. WILLSEY[5], R. J. G. VAN SLOUN[7], N. SHLEZINGER[8], P. G. PATIL[6], C. A. CHESTEK[4];
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Abstract: People with spinal cord injuries often need to rely on others for basic tasks, which limits their independence. A potential solution to this issue lies in brain-machine interfaces (BMIs), which enable patients to interact with devices, such as a computer or a robotic arm. These interfaces work by using decoding algorithms to process the patients' neural activity and predict control inputs. Traditional linear decoder algorithms, such as the Kalman filter, have been reliable due to their explainability: understanding the relationship between input and output promotes safety by preventing unexpected behaviors. However, linear decoders struggle to model the likely non-linear relationship between neural activity and movement. In contrast, deep learning algorithms show promising results but raise safety concerns due to their 'black-box' nature, limiting their use in controlling physical devices. Recently, KalmanNet was proposed as a way of combining the advantages of deep learning and the explainability of the Kalman filter by using a neural network to compute the Kalman gain (Revach et al., IEEE Trans. Signal Process, 2022). In this study, we adapted and applied KalmanNet for BMI applications.A rhesus macaque with microelectrode arrays implanted in the primary motor cortex was trained in a dexterous finger task, while finger kinematics and neural activity were recorded. Both offline (pre-recorded data, n = 3 days) and online (closed-loop control, n = 2 days) trials were conducted to compare KalmanNet's performance against the traditional Kalman Filter. The parameters for both models

were trained daily with a single 500-trial calibration run.In offline trials, KalmanNet achieved a significantly higher correlation with the actual velocities (112% increase, p<1E-4), indicating a more accurate movement prediction. During the online trials, KalmanNet increased throughput (28% increase, p<1E-7), reduced the orbiting time (71% reduction, p<1E-20), and shortened the time to target (19% reduction, p<1E-4), all indicative of improved performance.KalmanNet's Kalman gain appeared to vary with the output velocities, going high for higher velocities and low for lower velocities. Thus, KalmanNet seems to act as a non-linear trust system that modulates the Kalman gain to trust the neural activity for higher velocities or the evolution model for lower velocities. These findings suggest that KalmanNet may offer significant performance improvements over the Kalman filter while maintaining most of its explainable structure and without increasing the need for data, making it an attractive alternative to existing decoding algorithms.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.01/BB2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant R35 NS097343

Title: The effect of lactate on neuronal activity in the stomatogastric ganglion of C. borealis

Authors: M. IVANOVA[1], *S. KEDIA[1], E. E. MARDER[2];
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Abstract: Lactate is known to be a source of energy for neurons and glial cells both in vertebrate and invertebrate animals. In mammalian systems, lactate is thought to be released by glia and utilized by neurons during the course of normal activity. Intracellularly, lactate is the product of glucose metabolism and feeds into the production of ATP. However, recent studies suggest that lactate concentration may also be a meaningful signal for various neural networks, changing their activity and adjusting it in response to stressful conditions. We used the *Cancer borealis* stomatogastric ganglion (STG) to study the effects of extracellular lactate on neuronal activity. We constructed a dose response curve for L-lactate (Concentrations 2.5mM, 5mM, 10mM, 15mM, 20mM) while measuring the activity of two rhythms - the pyloric rhythm which is a constant rhythmic motor output, and the gastric rhythm which is stimulated by the presence of food. Another energy source - glucose - has been previously shown to increase pyloric activity in the STG. In contrast, different concentrations of lactate led to a small slowing of the pyloric

rhythm frequency while simultaneously triggering activity in the gastric neurons in a few preparations. We also noted a dramatic loss of activity and crash when lactate was washed out followed by a large rebound recovery in several preparations. The effects were exaggerated in the absence of neuromodulatory inputs. These results suggest that lactate acts not only as a fuel but also as a distinctive signal for this network. Overall, our results imply that lactate can modulate normal rhythmic activity of stomatogastric nervous system and affect its firing after withdrawal.

Disclosures: M. Ivanova: None. **S. Kedia:** None. **E.E. Marder:** None.

Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.02/BB3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R35 NS097343

Title: Regulating neuronal activity via ATP-sensitive potassium channels in the C. borealis stomatogastric ganglion

Authors: S. KEDIA[1], *N. ROMANO[1], E. E. MARDER[2];
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Abstract: Neuronal activity is dependent on intracellular ATP to regulate membrane potentials in conditions of ion fluxes, and to facilitate synaptic release. Prolonged changes in neuronal activity are hence likely to produce significant alterations in energy demand and usage. The altered availability of ATP has the potential to serve as a sensor for neurons signaling large deviations from their activity set points. We explore the effects of pharmacological manipulations of ATP-sensitive potassium channels on neuronal activity in the stomatogastric ganglion (STG) of the crab, *Cancer borealis* as a means to examine the interplay between ATP levels and activity. These channels have been studied for their role in neuroprotection and nutritional state signaling. In rhythmically bursting neurons in mammals, K-ATP channels are hypothesized to enable the transition between tonic firing and bursting states. We find channel modulation can impact rhythmic motor neuron activity bidirectionally in the STG. Diazoxide is a K-ATP channel opener and its application can stop action potentials and slow wave membrane potential oscillations in PD neurons. Channel closers, glibenclamide and tolbutamide, increase activity measured by frequency of bursting and action potentials. We investigated these effects further through dose response curves of the channel agonist and antagonist to construct the potential effects of smoothly transitioning ATP levels on network activity. We report the effects of channel activity of the spike and oscillation thresholds of bursting neurons and the characterization of the conductance impacted by the pharmacological agents we used. We find

that intracellular ATP levels can play a major role in regulation neuronal activity in the STG via K-ATP channels and that this pathway is variable across animals.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF IOS-1856433
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Title: The combinatorial effects of global perturbations, specifically extracellular saline concentration and temperature, on the nervous system of the lobster, Homarus americanus

Authors: *K. L. CARRIER, P. S. DICKINSON, Y. ALTUG, R. JANMOHAMED, I. KANE, D. J. POWELL;
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Abstract: As a result of climate change, ocean temperatures are rising, and areas of saltier water are becoming saltier while fresher areas become fresher. Amplification of the global water cycle, in part defined by altered patterns of precipitation, has caused saline concentrations to become more extreme. Simultaneously, temperatures have been and are expected to continue rising in both surface waters and in bottom coastal waters.As these trends continue to affect the marine ecosystem, it is of interest to examine the ability of marine organisms to withstand these environmental stressors and to characterize responses to such changes. That these organisms' neural circuits are robust to perturbation is of primary importance, as survival often depends on their continued function. These changes are problematic for the nervous systems of marine osmoconformers and pokiotherms because alterations to extracellular ionic concentrations and temperature can fundamentally affect neuron function. Furthermore, global perturbations, such as temperature and saline concentration, affect all biological processes governing nervous system function. The ability of a nervous system to continue functioning in the face of these challenges is non-trivial and remains an open question in the field.Using the stomatogastric nervous system (STNS) of the American lobster (*H. americanus*), we establish the upper limit of temperatures that neurons within the pyloric circuit, a central pattern generator that controls movements of the foregut required for digestion, can withstand without "crashing" (ceasing function but recovering when returned to normal conditions). We determine this temperature in normal (1x) physiological saline and then determine whether combinatorial changes in temperature and salinity concentrations change the limits of temperature tolerance when the perturbations occur

together. To test this, we subjected the STNS to increases in saline temperature until it crashed at 1x saline, and again at either an increased (1.25x) or decreased (0.75x) concentration. We find that the system is better able to withstand higher temperatures upon exposure to lower saline concentrations.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.04/BB5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish research council 2020-03365
Ragnar Söderberg foundation 1235/17
Swedish Foundation for Strategic Research FFL18-0112

Title: Heads or tails: dmrt3 and wt1a di6 interneurons shape fast and slow escape response in larval zebrafish

Authors: *H. K. KONING, A. B. I. GONZALEZ, A. AHEMAITI, A. DEL POZO CANO, A. D. PIZARRO, R. MANUEL, H. BOIJE;
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Abstract: To study how hardwired neural networks are able to generate a flexible behavioural output we turned to escape responses in larval zebrafish. The circuitry underlying larval escape behaviour is relatively simple and motor output consist of highly stereotyped swims, making it an eminent model to discern the role of individual neurons within the network. We focus on two closely related Contralateral Local (CoLo) interneuron types arising from the dI6 lineage. Both occur as a singlet per spinal hemi-segment and project contralaterally. The CoLo interneuron marked by dmrt3 expression are coupled to the Mauthner cell by gap junctions and inhibit contralateral motor neurons during the initial bend of escape swims. The second, newly identified CoLo type, marked by wt1a expression, does not have gap junctions to the Mauthner cell and it is distinct from its dmrt3 counterpart concerning morphology and electrophysiological properties. In this study we use morpholino knock-down and fictive locomotion, combined with a paradigm of head and tail stimulus evoked escape swims to sift out the functional role of dmrt3 and wt1a CoLo neurons within the escape network. While dmrt3 CoLo neurons seem to be involved in fast escapes, triggered by tail stimuli, wt1a CoLo neurons play a role in slower directional escape swims, elicited by head stimuli. These findings suggest that different motor programs might be orchestrated by distinct networks.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.05/BB6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS125362
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Project ALS

Title: Ventral spinocerebellar tract neurons utilize different connexins for their electrical connections during early development in the mouse spinal cord

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Abstract: Locomotion is generated by the central pattern generator and is responsible for the generation of rhythmic and alternating limb movements. In our lab, we identified ventral spino-cerebellar tract neurons (VSCTs) as necessary and sufficient neurons to drive generation and maintenance of locomotor behavior in mice. We also reported that VSCTs are electrically coupled amongst themselves as well as with spinal motor neurons. To reveal the molecular and cellular mechanisms involved in electrical coupling in VSCT neurons, we performed dual whole-cell patch clamp recordings, together immunohistochemistry and confocal microscopy. We investigated which connexins (Cx) mediate electrical coupling in VSCTs. Our strategy was based on previous reports of expression of Cxs 36, 37, 40, 43 and 45 in the developing spinal cord. We found that Cx37 and Cx40 were present on the soma and dendrites of VSCTs in postnatal P4-P5 mice. Cx36 and Cx43 were not present in VSCTs, while the presence of Cx45 remains to be resolved. To label the somato-dendritic morphology of VSCTs and uncover points of contact either amongst VSCTs or between VSCTs and motor neurons, we injected rAAV6/ds-CBH-GFP in hindlimb muscles to label motor neurons. In parallel, VSCTs were labelled by injection of CAV2-Cre virus into the cerebellum of floxed-TdTomato mice, resulting in their full somato-dendritic morphology. Confocal microscopy analysis revealed that Cx37 was observed in dendro-dendritic interactions solely amongst VSCT neurons. In contrast, Cx40 was observed in putative points of contact between VSCTs and motor neurons only.
These results identify the gap junctions responsible for electrical coupling in VSCT neurons and raise the possibility that Cx37 may be an essential protein amongst VSCTs, needed for their ability to participate in rhythmogenic activity during locomotor behavior.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.06/BB7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant T32 NS121768
NIH Grant R01 NS130799

Title: Postnatal development of 'rhythmogenic' currents and ion channels in spinal Shox2 interneurons

Authors: *S. SINGH, N. A. SHEVTSOVA, I. A. RYBAK, K. J. DOUGHERTY;
Dept. of Neurobio. and Anat., Drexel Univ., Philadelphia, PA

Abstract: Rhythmicity is a central feature within the neural underpinnings of everyday behaviors, including locomotion. Locomotion is performed rhythmically by organisms throughout life, despite developmental changes in cellular properties and neural connectivity. Rhythmic firing in the central nervous system is thought to be generated through a balance of network and intrinsic cellular properties. Within spinal locomotor circuitry, we have yet to determine which properties of spinal interneurons (INs) are involved in rhythmogenesis and how they change during development. Prior work from the lab has shown that gap junctional coupling between Shox2 INs likely contributes to rhythmic activity during fictive locomotion in neonatal mice but declines with age and is undetectable by adulthood. However, Shox2 INs in the adult spinal slice can be rhythmically active, and this spontaneous rhythmicity is absent in neonatal Shox2 INs. We therefore hypothesize that the magnitude of 'rhythmogenic' ionic currents and the expression of the corresponding voltage-gated ion channels increase in putative rhythm generating INs during postnatal development. Here, we have combined whole cell patch clamp recordings, immunohistochemistry, and RNAscope targeting lumbar Shox2 INs to study the properties of putatively rhythmogenic ionic currents and the expression of corresponding ion channels in Shox2 INs across postnatal time points in mice. We show that subsets of Shox2 INs possess a set of currents which may shape rhythmic bursting. They include persistent inward currents (PICs), M-type potassium currents, and slow afterhyperpolarization (sAHP). PICs and M currents were seen with high prevalence in all age groups examined and increase in magnitude with age. However, sAHP is rarely present in neonatal Shox2 INs but is present in about half of juvenile and adult Shox2 INs. The amplitude of the PIC was decreased using riluzole or nimodipine, suggesting the presence of sodium and calcium components. Subsets of Shox2 INs indeed possess RNA transcripts for $Na_V1.6$ and $Ca_V1.3$. Additionally, a subset of Shox2 INs possess SK2 and SK3, two small conductance calcium-activated potassium channels that mediate sAHP. $K_V7.2$ & $K_V7.3$ voltage-gated ion channels, which mediate M-type potassium currents, were expressed at high rates in Shox2 INs overall and showed a marked increase by adulthood. These data suggest a developmental shift in the magnitude of rhythmogenic ionic currents and the expression of corresponding ion channels. Findings from this study will inform future experiments to reveal essential mechanisms of locomotor rhythmogenesis in mature spinal locomotor circuitry.

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Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

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Program #/Poster #: PSTR089.07/BB8

Topic: E.07.a. Cellular properties – Interneurons and motor neurons

Support: CIHR grant 180522
CIHR grant 14392

Title: Brainstem regions activated during cortical stimulation-induced mastication and electrical stimulation of trigeminal sensory afferences in mice.

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Abstract: Mastication is a vital behaviour. While this rhythmic movement can be initiated by the repetitive stimulation of the cortical masticatory area (CMA) or the sensory trigeminal afferences, the rhythmic patterns of the movement are established and maintained by the coordinated activity of the masticatory central pattern generator (CPG) located in the brainstem, between the rostral poles of the facial (NVII) and the trigeminal (NVmt) motor nuclei. The trigeminal main sensory nucleus (NVsnpr), whose neurons can change their firing pattern from tonic to rhythmic bursts has recently been thought to form the rhythmogenic core of the masticatory CPG because rhythmic firing of its neurons drives rhythmic responses in NVmt. However, previous studies in rat, guinea pig and rabbit have shown that, besides NVsnpr, premotor interneurons in the peritrigeminal area (PeriV) and the oral division of the spinal trigeminal nuclei (NVspo) may also contribute to the masticatory circuitry.The aim of this study is to confirm these findings in a mouse model and to further precise the role of PeriV interneurons in the production and transformation of rhythmic patterns by stimulation of the peripheral or cortical inputs. Here, right unilateral 40Hz optogenetic stimulation of the cortical masticatory area (CMA) triggered rhythmic jaw movements in Thy1-ChR2 and VGlut2-ChR2 awake mice. In both cases, following a protocol of 3 s stimulations every 30 seconds for 30 minutes, preliminary data of c-fos cell staining revealed a significantly higher activation in specific PeriV areas; the juxtatrigeminal area (JuxtV), medial to the NVmt and the parvicellular reticular nuclei (PCRt), ventral to the NVmt, as well as in the trigeminal accessory nucleus (NVacc). However, surprisingly little c-fos labelling was found in NVsnpr. In a second of experiments, using Ca^{2+}-imaging in slices of VGlut2-GCamp6f mice, we found that electrical stimulation of the trigeminal sensory afferences induced Ca^{2+} responses in NVsnpr, NVmt and

PeriV (mainly in the supratrigeminal region (SupV) and the PCRt). Induction of rhythmic bursting in NVsnpr (with localized BAPTA applications) also triggered rhythmic responses in NVmt, SupV and PCRt. These results suggest that different areas may be involved in triggering mastication depending on the input (cortical vs sensory) and that PeriV may significantly contribute to transmission or modulation of the pattern of orofacial movements.

Disclosures: O. Sanvi: None. **D. Falardeau:** None. **S. Dubois:** None. **A. Kolta:** None.

Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.08/BB9

Topic: E.07.a. Cellular properties – Interneurons and motor neurons

Support: RF1NS118606

Title: Different mechanisms contribute to the initiation and maintenance of feeding-related behaviors in the mollusc Aplysia

Authors: *C. G. EVANS[1], M. A. BARRY[1], Q. CHEN[1], C. N. REAVER[1], M. H. PERKINS[1], J. JING[1,2], E. C. CROPPER[1];
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Abstract: Higher order projection neurons play an important role in initiating activity and have been the subject of much investigation. Relatively few studies have, however, characterized firing patterns of these cells during normal behavior. We address this issue focusing on the cerebral buccal interneurons (CBIs), which trigger feeding related behaviors in *Aplysia*. In reduced 'intact head' preparations there are decreases in CBI activity as feeding progresses (e.g., Jing 2005). This has been shown for 5/~13 CBIs. To determine whether these results reflect the activity of the population as a whole, we developed techniques that we used to record CBI activity in whole animals ingesting seaweed. We observed decreases in the CBI firing frequency similar to those described in reduced preparations. To verify that reductions in firing frequency occurred while motor activity was still ongoing, we simultaneously recorded from buccal nerve 3 (BN3) in one set of animals, and from BN3 and the buccal end of the severed esophageal nerve in a second set. In both cases bursts of nerve activity were observed after CBI activity declined. This suggests that as feeding progresses there are changes in the mechanism that drives motor activity. Peptides released when the CBIs are active increase the excitability of a buccal ganglion neuron that is important for initiating motor programs (B63) (Due et al. 2022). We now show that peptides that modify intrinsic properties of B63 induce an inward current that may be similar to one that induces oscillatory activity in other species (i.e., I_{MI}). The induction of this current may facilitate program initiation after CBI activity decreases. To determine whether the duration of activity remains under stimulus control we tested the idea that it is driven by afferent feedback from the gastrointestinal system. We recorded from BN3 in; (1) animals that were fed seaweed

(mechanical and chemical gut stimulation), (2) animals that were fed paper (mechanical gut stimulation), and, (3) animals in which we induced feeding responses but did not allow food ingestion (no gut stimulation). With only mechanical gut stimulation there were fewer bursts of activity in BN3. With no gut stimulation there was virtually no BN3 activity. This suggests that input from chemoreceptors in the gut plays a role in generating the activity that continues after CBI activity declines. Our data support the idea that although initial ingestive movements are driven by the activity of higher order projection neurons, as feeding progresses, there are reductions in the activity of these cells and behavior is primarily maintained by afferent input from the gastrointestinal system.

Disclosures: C.G. Evans: None. **M.A. Barry:** None. **Q. Chen:** None. **C.N. Reaver:** None. **M.H. Perkins:** None. **J. Jing:** None. **E.C. Cropper:** None.

Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.09/BB10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Stichting Incontinence Foundation

Title: Neural architecture of the midbrain periaqueductal gray

Authors: *H. H. SUBRAMANIAN[1], R. J. BALNAVE[2], G. HOLSTEGE[3];
[1]Boston Scientific, Valencia, CA; [2]The Univ. of Sydney, Sydney, Australia; [3]emeritus Professor, Groningen Academic Hosp., Haren, Netherlands

Abstract: The midbrain PAG is a critical relay center of the emotional motor system and controls neural circuits that regulate breathing, blood pressure, bladder function, vocalization, coughing, sneezing, vomiting and maintenance of abdominal and intrathoracic pressure. Dysfunction of PAG circuits lead to dysreflexia such as dyspnea, ataxic breathing, hyper & hypotension and micturition disruption (urinary incontinence).
Circuit specific neuromodulation of the PAG could reverse specific types or combined dysfunctions paving way for development of neurologic clinical therapy.
However, PAG circuit dynamics are unkown.
For this reason, we stereotaxically mapped the PAG in the rat in vivo to investigate its neural architecture, circuit physiology and anatomical topography.
The PAG was found to be predominantly quiescent in the resting state and could be activated by iontophoresis of excitatory amino acid glutamate agonists. Cells activated ceased function when glutamate ejection was terminated or by co-iontophoresis of muscimol (GABA agonist). Very few spontaneously active cells were found in the PAG, mainly in its dorsal region and these cells, typically fired in a slow and irregular pattern. Activation of either behavioral and/or emotional motor interventions caused immediate activation of PAG neurons mainly in the lateral

and ventrolateral PAG. showing two distinct types of activity patterns; 1) single spike firing and 2) burst firing, The cells fired both tonically and phasically when correlated with specific emotional motor output such as the diaphragm EMG. Predominantly the non-bursting PAG neurons had a near normal distribution around 200 to 250 msec, while burst-firing cells typically showing a bimodal distribution. The functional implications of PAG neuronal activity are discussed in terms of descending motor and emotional motor control and effective translation for application of neuromodulation clinical therapy for specific emotional motor diseases.
Acknowledgement and DeclarationThe animal studies were undertaken by HHS, RJB and GH wholly at The University of Sydney & University of Groningen under the respective institutional ethics approvals. HHS, RJB and GH designed the project, performed the experiments, analyzed primary data and made figure illustrations. GH curated and approved the final data/figure representation in this presentation/poster. None of work described here were undertaken at the current work designation of Hari Subramanian.

Disclosures: H.H. Subramanian: None. **R.J. Balnave:** None. **G. Holstege:** None.

Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.10/BB11

Topic: E.07.a. Cellular properties – Interneurons and motor neurons

Support: R21 NS118226
R01 NS104194
T32 NS121768

Title: Molecularly diverse glycinergic interneurons within medial laminae V/VI inhibit Shox2 interneurons in the lumbar spinal cord

Authors: *J. R. MCGRATH, D. DAYO, D. GARCIA-RAMIREZ, K. J. DOUGHERTY; Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) disrupts descending control of spinal circuitry, often leading to severe locomotor deficits. Essential locomotor circuits that generate both the rhythm and pattern of locomotion are located in the lumbar segments of the spinal cord; thus, below most SCIs, and relatively intact after injury. A population of locomotor circuit interneurons (INs) identified by the transcription factor Shox2 is involved in both rhythm generation and pattern formation, providing a possible access point to control locomotor function. Efforts to improve locomotor recovery after SCI, such as epidural stimulation (ES), target the locomotor circuits via the activation of sensory afferents. Afferent pathways to Shox2 INs have been shown to be either excitatory or inhibitory in near equivalent proportions. However, in chronic complete SCI, there is an excitatory shift in afferent input to Shox2 INs. Recent data from our lab demonstrates that treatment with sub-motor-threshold ES restores sensory-evoked inhibitory input to Shox2 INs.

This suggests that a population of inhibitory INs involved in sensory afferent pathways to Shox2 INs are a novel point of plasticity, and a potential therapeutic target following SCI. In this study, we aim to identify molecular markers that label inhibitory INs interposed in sensory pathways to Shox2 INs. Triple transgenic mouse lines that label inhibitory neurons (either GAD67-GFP or GlyT2-GFP) and Shox2 INs (Shox2cre; R26-lsl-tdTomato) were used to test for connections between the two populations. Lumbar spinal slices from neonatal mice in each transgenic line were used and inhibitory neurons were stimulated pharmacologically by picospritzing of kainate, during simultaneous whole cell patch clamp recordings of single Shox2 INs. We found that glycinergic neurons are more likely to be connected to Shox2 INs than GABAergic neurons, and glycinergic neurons with connections are largely restricted to medial laminae V/VI. This region coincides with an area containing dense parvalbumin labeling, indicating that it is a termination zone of proprioceptive afferent terminals. Antibodies to known molecularly-defined populations within laminae V/VI were used to evaluate the overlap with glycinergic neurons in this region. No single molecular marker labels all of the glycinergic neurons in medial laminae V/VI but at least three markers show partial overlap with the laminae V/VI glycinergic neurons in this region. These findings identify a molecularly diverse population of glycinergic neurons that are presynaptic to Shox2 INs and potentially involved in the inhibitory control of Shox2 INs by low threshold afferent pathways.

Disclosures: **J.R. McGrath:** None. **D. Dayo:** None. **D. Garcia-Ramirez:** None. **K.J. Dougherty:** None.

Poster

PSTR089. Cellular Properties: Interneurons, Premotor, and Motor Neurons

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.11/BB12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH NS104194
NIH NS130799

Title: Serotoninergic modulation of spinal ROR-Beta interneurons in the medial deep dorsal horn.

Authors: *C. W. WEST, D. L. GARCIA-RAMIREZ, K. J. DOUGHERTY;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) involves damage to descending projections which causes not only paralysis, but also spasticity and hyperreflexia. Descending projections from the brainstem raphe nucleus release serotonin into the spinal cord. Serotonin has strong modulatory effects on primary afferent depolarization (PAD), which is associated with the regulation of the sensory afferent transmission that evoke reflexes. Serotonin modulates both primary afferent terminals and unidentified interneurons (INs) in the deep dorsal horn. However, the modulatory actions of

serotonin on specific IN populations that produce PAD are not yet understood. Thus, to best develop therapeutics for hyperreflexia and spasticity after SCI, it is important to understand how descending serotonin modulates the specific INs that regulate afferent transmission. In this study, we aim to determine how serotonin modulates RORβ INs, a GABAergic IN population in the medial deep dorsal horn that regulates the transmission of proprioceptive sensory afferents. We used spinal slices from young (1-3 week old) uninjured male and female RORβcre::R26-lsl-tdTomato mice to perform whole cell patch clamp recordings from visually-identified RORβ INs in medial deep dorsal horn. We measured changes in the electrophysiological properties of RORβ INs in response to application of 10μM serotonin. Serotonin leads to a depolarization of the membrane potential of RORβ INs, along with an associated increase in the action potential firing frequency. In addition, there is an increase in the spontaneous postsynaptic inputs to RORβ INs during application of serotonin. These findings provide evidence for excitatory modulation of RORβB neurons by serotonin. In the context of recent studies suggesting that PAD facilitates afferent transmission, together with known inhibitory modulation of afferent terminals by serotonin, our results contribute to the understanding of the precise circuit elements involved in the neuromodulatory control of proprioceptive afferent transmission. A detailed understanding mechanism of the regulatory controls of proprioceptive afferent transmission may eventually be leveraged to reduce hyperreflexia after SCI.

Disclosures: C.W. West: None. **D.L. Garcia-Ramirez:** None. **K.J. Dougherty:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.01/BB13

Topic: F.01. Neuroethology

Support: UVA Start-up

Title: Seasonal plasticity of astrocytes in the avian song control circuit

Authors: *W. C. TUCKER[1,2], S. L. SHEPHARD[2], J. M. BOYD[2], A. J. PEREZ[2], T. LARSON[2,1];
[2]Biol., [1]Univ. of Virginia, Charlottesville, VA

Abstract: Understanding regulation of adult neurogenesis and the involvement of other brain cell types is vital to reducing the burden of neurodegenerative disease. Specifically, astrocytes are involved in adult neurogenesis and support developing and mature neurons, as well as participate in refinement of neural circuits during development. The Gambel's white-crowned sparrow (Zonotrichia leucophrys gambelli) is a well-established model in the study of adult neurogenesis, as functional new neurons are added to a neural region responsible for singing behavior, called HVC, in an extreme and cyclical manner based on seasonal conditions. The temporal dynamics of astrocyte birth, maturation, and survival during cycles of extreme

degeneration and regeneration, in addition to the mechanisms regulating these dynamics, remain uncharacterized in the songbird brain. Here, we examine the number of astrocytes in breeding and nonbreeding conditions and find that astrocytes display seasonal plasticity in number and maturation. Using BrdU pulse-chase methods combined with lineage-specific markers to assess new cell identity, maturity, and plasticity during and after HVC seasonal degeneration, we find that astrocytes turn over during HVC degeneration. Our results suggest a possible role of adult-born astrocytes in supporting a return to homeostasis following extensive neuronal loss in HVC. Characterization of astrocyte dynamics during HVC degeneration and regeneration will allow further inquiry and understanding of the functional role of these astrocytes in neural plasticity.

Disclosures: W.C. Tucker: None. **S.L. Shephard:** None. **J.M. Boyd:** None. **A.J. Perez:** None. **T. Larson:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.02/BB14

Topic: F.01. Neuroethology

Support: UVA Startup Funds

Title: Rapidly shifting dynamics between cell generation and survival during natural regeneration of a sensorimotor nucleus in songbirds

Authors: *C. S. MULLINS[1], E. A. SCALZI[1], M. DOWNES[2], A. COCHRANE[2], T. A. LARSON[2];
[1]Univ. of Virginia Neurosci. Undergraduate Program, Charlottesville, VA; [2]Univ. of Virginia Dept. of Biol., Charlottesville, VA

Abstract: Seasonally breeding songbirds exhibit rapid changes in neuronal birth, incorporation and survival, which coincide with the production of high-quality singing behavior. The rapid growth of neural tissue must then stabilize to prevent overgrowth and maintain singing behavior. Thus, it is important to understand the dynamics in cellular number and behavior that contribute to both growth and maintenance of the neural tissue. Here, we induce breeding physiological conditions of the songbird Gambel's white-crowned sparrow (*Zonotrichia leuchophyrs gambelli*) to promote the seasonal addition of new neurons into the song control brain region called HVC. We examine the temporal dynamics of neuronal birth, addition, and death in addition to microglia numbers and behavioral states throughout the time course of HVC growth and homeostatic stabilization. We found that most new neurons are added to HVC between 4-14 days into breeding conditions. Contrary to expectations, proliferation of the neural progenitor cells (NPCs) that contribute new neurons to HVC remains low during HVC growth, and, in fact, neurons added to HVC are born 14-21 days prior to the onset of breeding physiology. These data suggest that the status of cell survival regulates NPC proliferation, possibly to limit excessive

production of new neurons and HVC overgrowth. We will test this new hypothesis by stimulating proliferation of NPCs during early HVC growth through pharmacological manipulation and examining whether or not ectopic proliferation can alter final HVC size or impact singing behavior. Our data provide insight into the dynamics within and across cell lineages during growth of neural tissue, as well as possible mechanisms that ultimately terminate regeneration to reestablish homeostasis and behavior.

Disclosures: C.S. Mullins: None. **E.A. Scalzi:** None. **M. Downes:** None. **A. Cochrane:** None. **T.A. Larson:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.03/BB16

Topic: F.01. Neuroethology

Support: UVA Start-up

Title: Unique modes of neural plasticity in two different "neurogenic" regions of the avian brain that contribute to distinct seasonal behaviors

Authors: *E. A. SCALZI[1], C. S. MULLINS[1], W. C. TUCKER[2], T. A. LARSON[1];
[1]Biol., Univ. of Virginia, Charlottesville, VA; [2]Biol., Univ. of Virgnina, Charlottesville, VA

Abstract: Resource allocation becomes important in brain regions undergoing dramatic, cyclical plasticity in size and cellular content, especially when these regions control behavior necessary for the life history of the organism. In Gambel's white-crowned sparrow (*Zonotrichia leucophrys gambelli*), the sensorimotor nucleus controlling seasonal singing behavior adds around 60,000 neurons to an existing pool of around 100,000 neurons, doubling the total volume of HVC, each breeding season. Upon transition into nonbreeding conditions, an equal number of neurons die off each year. Lying immediately across the ventricle of HVC is the hippocampus, another brain region that is capable of adding adult-born neurons and that is important for spatial navigation such as that during seasonal migration. We hypothesized that in songbirds hippocampus might grow just prior to the onset and after the end of breeding season to accommodate both the need for migratory behavior and for the conservation of space and other resources in the telencephalon. Quantification of hippocampal volume and neuron number, however, revealed that hippocampus is not plastic in volume across seasons. Rather, the total volume of the telencephalon appears to expand slightly during growth of HVC. Although not plastic in total volume, hippocampus does change seasonally in cellular content: both astrocytes and neurons appear to turnover at higher rates upon entry into breeding condition. These data suggest that different "neurogenic regions" of the avian telencephalon achieve seasonal plasticity in cytoarchitecture through different means all the while still contributing to seasonal behavior like singing and migration. Uncovering mechanisms in the avian brain that allow for extreme growth

without cost to other brain regions or behavior will lay the foundation for understanding the mechanisms controlling morphology and resource allocation during both early neural development and adult plasticity.

Disclosures: E.A. Scalzi: None. **C.S. Mullins:** None. **W.C. Tucker:** None. **T.A. Larson:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.04/BB17

Topic: F.01. Neuroethology

Support: UVA Start-up

Title: Relative contribution of neuronal and astroglial death in driving reactive proliferation of neural progenitor cells

Authors: K. Y. CHUNG, M. A. GUAJARDO, J. M. BOYD, W. C. TUCKER, *T. LARSON; Biol., Univ. of Virginia, Charlottesville, VA

Abstract: The sensorimotor nucleus responsible for singing behavior in the songbird Gambel's white-crowned sparrow (*Zonotrichia leucophrys gambelli*) - called HVC - exhibits dramatic seasonal plasticity in both morphology and cytoarchitecture between breeding and nonbreeding seasons. As male sparrows transition into breeding physiological conditions, their HVC nearly doubles in neuron number and total size. Upon transition into nonbreeding seasons HVC rapidly degenerates in neuron number and size. This natural form of degeneration induces neural progenitor cells in the nearby ventricular zone to rapidly proliferate. Preliminary data suggests that in addition to the known neuronal death, astrocytes also die during HVC degeneration. These new data prompt the question: the death of which cells - neurons, astrocytes, or both - drive reactive proliferation? To determine the relative contribution of each cell type's death to reactive proliferation, we selectively ablated neurons, astrocytes, or both in HVC of individual birds in both breeding and nonbreeding conditions through excitotoxic pharmacological manipulations. We explored the time course of cell death and reactive proliferation, in addition to the response by microglia - a cell type known for clean-up of dead cells and to be necessary intermediaries between HVC cell death and reactive proliferation. Uncovering which cells stimulate reactive proliferation through their death and the temporal dynamics of response to this cell death will lay the groundwork for addressing the fundamental question of the function of reactive proliferation in addition to uncovering underlying mechanisms that promote proliferation following neural degeneration.

Disclosures: K.Y. Chung: None. **M.A. Guajardo:** None. **J.M. Boyd:** None. **W.C. Tucker:** None. **T. Larson:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.05/BB18

Topic: F.01. Neuroethology

Support: NIH Grant NS104008

Title: Characterization of dopaminoceptive cells in song control nuclei of canaries and their activation during song production

Authors: C. M. HAAKENSON[1], J. H. BALTHAZART[2], J. W. VANRYZIN[3], A. E. MARQUARDT[4], S. E. ASHTON[4], M. M. MCCARTHY[4], *G. F. BALL[5];
[1]Neurosci. and Cognitive Sci. Program, Dept. of Psychology, Univ. of Maryland, Col. Park, College Park, MD; [2]Giga Neurosciences, Univ. of Liege, Liege, Belgium; [3]Dept. of Pharmacol., [4]Univ. of Maryland Sch. of Med., Baltimore, MD; [5]Psychology, Univ. of Maryalnd, College Park, MD

Abstract: It has been hypothesized for well over 30 years that catecholamine systems project to forebrain song control nuclei. Projections from catecholaminergic cell groups and receptor distribution have also been characterized but the distribution and role of the different dopamine receptors remain poorly understood. Sensitive in situ hybridization procedures (employing RNAScope methods) were used here to quantify the expression of 3 dopamine receptors (DRD1, DRD2 and DRD3) in two song control nuclei (HVC and Area X of the basal ganglia) and in the periaqueductal gray (PAG) of male and female canaries. Both sexes were treated with Silastic implants filled with testosterone to ensure they would produce song. We also determined the excitatory (co-expression of VGlut) or inhibitory (co-expression of GAD) nature of the cells expressing these receptors as well as their activation as measured by the expression of EGR1 following a 30 minute period of song production. The three receptor types were identified in each brain area with the exception of DRD3 in Area X, but the density of cells expressing the three receptors varied as a function of the receptor type and of the brain area. Very few sex differences were detected. Overall the density of cells positive for DRD was much lower in PAG than in the two song control nuclei. In HVC, the majority of cells (88%) were VGlut-positive for the three receptors subtypes, in contrast to the low percentage in Area X (6%) and intermediate in PAG (50%). The percentage of dopaminoceptive cells expressing GAD was much more limited (20% in HVC, 5% Area X, 21% PAG). Most dopaminoceptive cells in Area X did not express either marker and therefore their neurochemical status remains uncertain. Finally, cellular activation during singing behavior, as measured by the expression of EGR1, was observed in different cells that each expressed one of the three dopamine receptors, with the exception of cells expressing DRD3 in the PAG. These results provide insight into the putative roles of dopaminoceptive cells in network excitation/inhibition dynamics, as these cells are primarily excitatory in HVC, and indicate that these cells are active during song production.

Disclosures: **C.M. Haakenson:** None. **J.H. Balthazart:** None. **J.W. Vanryzin:** None. **A.E. Marquardt:** None. **S.E. Ashton:** None. **M.M. McCarthy:** None. **G.F. Ball:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.06/BB19

Topic: F.01. Neuroethology

Title: The development of synapses in the syrinx diverges at the onset of sexually dimorphic vocalization in the zebra finch songbird (Taeniopygia guttata)

Authors: *J. V. GOGOLA[1,5], D. MARGOLIASH[2,3], N. B. KASTHURI[4,5];
[2]Organismal Biol. and Anat., [3]Psychology, [4]Neurobio., [1]Univ. of Chicago, Chicago, IL;
[5]Argonne Natl. Lab., Lemont, IL

Abstract: Songbirds have long been central to the study of vocal learning and production, and in most species, males and females sing. However, in the best-studied species, the zebra finch (*Taeniopygia guttata*), only males sing. Most theories of this sexual dimorphism had suggested that male zebra finches have specializations, e.g. to promote song, that females do not. We recently found the opposite. At the synapses that connect motoneurons to muscle fibers (neuromuscular junctions; NMJs) of the avian voicebox (syrinx, analogous to larynx), we found female synaptic specializations that support song suppression: Female syrinx, and only female syrinx (not tongue, *latissimus dorsi*, or any male muscle measured) has specialized NMJs that could work to suppress singing ability in this species. Specifically, the female syrinx shows a high proportion of weaker NMJs, biased towards smaller and weaker muscle fibers, which fail to form a motor endplate band (MEB). However, these results raise an unanswered question: are male and female syringes born different, or do they have divergent developmental programs? We analyzed male and female (n=3) across key ages - the robust onset of sensory song learning (post-hatch day P30), song-like vocalizations (P50), and the end of sensorimotor learning (P70). We used immunofluorescence to label motoneuron axons (neurofilament), NMJs (α-bungarotoxin), and muscle fiber type (Fast vs Superfast; MY-32), and measured NMJ area, class (stronger *en plaque "enPl"* vs weaker *en grappe "enGr"*), and spread across the length of muscle fibers. We find that NMJs in male and female syrinx muscles are similar early in development and then diverge. At P30, males and females show similar proportions of *enPl* and *enGr* NMJs, shifting with age to primarily *enPl* in males but unchanged in females. We see a rudimentary MEB at P30 in both sexes primarily composed of *enPl* NMJs, which becomes more centralized over age. However, development outside the MEB region is sexually dimorphic. At P30, both sexes have both classes of NMJ outside the MEB region. By P50, both sexes begin losing extra-MEB *enPl* NMJs, but by P70, most male *enGr* NMJs have been lost throughout the muscle while females have solely *enGr* NMJs outside of the MEB. Additionally, male *enGr* NMJs in this region have become smaller while those in the females have become larger. Thus, we conclude that adult sexual dimorphisms are the result of a common early developmental program that

diverges around the onset of singing - male synaptic development promotes singing, while female synaptic development suppresses singing.

Disclosures: **J.V. Gogola:** None. **D. Margoliash:** None. **N.B. Kasthuri:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

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Topic: F.01. Neuroethology

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NIH Grant GM120464
NSF Graduate Fellowship DGE-1448072

Title: Sex and age effects on the transcriptome of zebra finch song nucleus RA

Authors: S. R. FRIEDRICH[1], A. NEVUE[2], A. ANDRADE[3], T. VELHO[3], ***C. MELLO**[4]; [1]Behavioral Neurosci., [2]Oregon Hlth. & Sci. Univ., Portland, OR; [3]Federal Univ. of Rio Grande do North, Natal, Brazil; [4]Behavioral Neurosci., Oregon Hlth. and Sci. Univ. Sch. of Med., Portland, OR

Abstract: The song control nuclei and related projections in zebra finches (*T. gutatta*), a songbird species where only males sing, are much larger in males than in females. While this is one of the most striking brain dimorphisms underlying sex differences in behavior, its molecular basis has remained largely unknown. We focused the present study on the robust arcopallial nucleus (RA), the source of the descending output of the cortical vocal pathway and a key player in encoding acoustic features of learned song. RA is monomorphic at 20 days post-hatch (dph), then atrophies in females and grows up to 7-fold larger in males by 50 dph. To explore the transcriptomic changes associated with this developmental sex difference, we performed bulk RNA-seq analysis of laser dissected RA samples from both sexes at these two developmental stages of the vocal acquisition period. We found that sex-differential gene expression in RA expands from hundreds of predominantly sex chromosome Z genes at 20 dph to thousands of autosomal genes by the time sexual dimorphism asymptotes at 50 dph. Male-specific developmental processes include cell and axonal growth, synapse assembly and activity, and energy metabolism; female-specific processes include cell polarity and differentiation, transcriptional repression, and steroid hormone and immune signaling. Evidence from transcription factor binding site analysis supports female-biased activation of pro-apoptotic regulatory networks. The extensive and sex-specific transcriptomic reorganization of RA provides insights into potential drivers of dimorphic neurodevelopment of the zebra finch song control system. To maximize data mining and further discovery, we developed apps that facilitate the visualization of sex and age effects on individual gene expression in RA, as well as

integration of these datasets with single cell transcriptomics and brain distribution patterns from the *in situ* hybridization gene expression brain atlas (ZEBrA: www.zebrafinchatlas.org).

Disclosures: S.R. Friedrich: None. **A. Nevue:** None. **A. Andrade:** None. **T. Velho:** None. **C. Mello:** None.

Poster

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Title: Sex similarities in song behavior, song system neuroanatomy, and immediate early gene expression in the red-cheeked cordon bleu

Authors: *E. M. ROSE[1], C. HAAKENSON[1], B. D. SHANK[2], G. F. BALL[1];
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Abstract: Sex similarities in song behavior, song system neuroanatomy, and immediate early gene expression in the red-cheeked cordon bleu
Rose, Evangeline M.[1,2]; Haakenson, Chelsea M. [1,2]; Shank, Benjamin D.[3] & Ball, Gregory F. [1,2]
1.Department of Psychology, University of Maryland, College Park, College Park MD
2.Program in Neuroscience and Cognitive Science, University of Maryland, College Park, College Park, MD, USA3.Department of Physics, Hope College, Holland, MIBirdsong is a well-studied behavior, both due to its importance as a model for vocal production learning in humans and other animals and as a fascinating complex social behavior. Historically, work on birdsong has tended to focus on males. However, it is now widely accepted that female song not only exists, but is likely ancestral in the oscine passerines. Establishing good models in the lab is critical for our understanding of sex-specific factors in the physiology controlling behaviors. In this study, we examined the brain and behavior of the red-cheeked cordon bleu (RCCB), an Estrildid finch species with extensive female song. First we characterized sex differences in circulating hormones and the song control system (SCS), a set of cytoarchitecturally discrete brain nuclei that regulate vocal learning, perception, and vocal production. First, we found that there were no significant sex differences in circulating levels of testosterone and progesterone. There were also no significant differences in cell densities in the three nuclei of the SCS we examined. The volume of the robust nucleus of the arcopallium was not significantly different and we report the smallest sex difference in HVC volume yet published in a songbird. Additionally, we demonstrated similar levels of motor driven immediate early gene expression in

both males and females after engaging in song. Finally, we characterized the acoustic structure of the vocalizations of both males and females. We found high inter-individual variation in song types but highly similar song rate and acoustic features between sexes.

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Topic: F.01. Neuroethology

Support: NSF grant IOS2154646

Title: Cell type specializations of the vocal-motor cortex in songbirds

Authors: A. NEVUE[1], B. ZEMEL[4], S. R. FRIEDRICH[2], ***H. VON GERSDORFF**[3], C. MELLO[5];
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Abstract: The identification of molecular specializations in cortical circuitry supporting complex behaviors, such as learned vocalizations, requires understanding the neuroanatomical context from which these circuits arise. In songbirds, the robust nucleus of the arcopallium (RA) provides the sole descending cortical projection for fine motor control of vocalizations, and plays key roles in encoding acoustic features of song. Using single nuclei transcriptomics and spatial gene expression mapping by *in situ* hybridization, we were able to define cell types and molecular specializations that distinguish RA from adjacent regions involved in non-vocal motor and sensory processing. Among main findings, we describe an RA-specific vocal projection neuron, differential composition of inhibitory neuron subtypes, and unique glial specializations. We also show how several of these cell-specific molecular features arise in a sex-dependent manner during development, by examining previously published bulk RNA-seq datasets (Friedrich et at., Cell Rep., 2021). Based on the molecular data, we were also able to electrophysiologically probe, for the first time, predicted GABAergic subtypes within RA, and have identified two morphotypes within the NPY+ subtype. To facilitate data mining and future discoveries, we have developed interactive apps that allow integration of cell level molecular data with developmental and spatial distribution data from our gene expression brain atlas (ZEBrA:www.zebrafinchatlas.org). With this resource, users can explore molecular specializations of vocal-motor neurons and support cells that likely reflect adaptations key to the physiology and evolution of vocal control circuits.

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Title: A predisposed motor bias shapes individuality in vocal learning

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Abstract: The development of individuality during learned behavior is a common trait observed across animal species; however, the underlying biological mechanisms remain understood. Similar to human speech, songbirds develop individually unique songs with species-specific traits through vocal learning. In this study, we investigate the developmental and molecular mechanisms underlying individuality in vocal learning by utilizing F_1 hybrid songbirds (Taeniopygia guttata cross with *T. bichenovii*), taking an integrating approach combining experimentally-controlled systematic song tutoring, unbiased discriminant analysis of song features, and single-cell transcriptomics. When tutoring with songs from both parental species, F_1 hybrid individuals exhibit evident diversity in their acquired songs. Approximately 30% of F_1 hybrids selectively learn either song of the two parental species, while others develop merged songs that combine traits from both species. Vocal acoustic biases during vocal babbling initially appear as individual differences in songs among F_1 juveniles and are maintained through the sensitive period of song vocal learning. These vocal acoustic biases emerge independently of the initial auditory experience of hearing the biological father's and passive tutored songs. We find individual differences in transcriptional signatures in the glutamatergic neurons projecting from the cortical vocal output nucleus to the hypoglossal nuclei, which are associated with variations of vocal acoustic features. These findings suggest that a genetically predisposed vocal motor bias serves as the initial origin of individual variation in vocal learning, influencing learning constraints and preferences.

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Poster

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Program #/Poster #: PSTR090.11/BB24

Topic: F.01. Neuroethology

Support: NIH Grant R01MH105519

Title: Dynamic changes in the neuronal structure of the Zebra Finch basal ganglia during vocal development and their regulation by miR-9

Authors: *H. JARRELL[1], M. HOROWITZ[2], Z. HUANG[1], Z. SHI[1], Y. DING[2], X. LI[1]; [1]Neurosci. Ctr., LSU Sch. of Med., New Orleans, LA; [2]Neurosci. Ctr., Tulane Univ., New Orleans, LA

Abstract: Male juvenile zebra finches learn to sing by imitating conspecific adult songs during a sensitive period of development early in life. Area X is a basal ganglia nucleus critical for song learning and maintenance. The majority of neurons in Area X are spiny neurons that receive inputs from cortical nuclei HVC and lMAN to form the cortical-striatal circuit necessary for sensory-motor song learning. The structural changes of spiny neurons during song development have previously been unknown. In this study, we examined spiny neuron structure at key stages of song development. We used a lentivirus expressing the fluorescent marker mCherry combined with antibody staining against DARPP-32 to sparsely label spiny neurons. We imaged neurons using confocal microscopy, traced their structure in 3-dimensions using the software Imaris, and quantified dendritic branch points, dendrite length, and spine density.We find that dendritic arborization and spine density of spiny neurons undergo growth and expansion during the sensitive period for song related sensory learning and peak at 60 d. This growth phase is followed by pruning of dendrites and dendritic spines and change in spine morphology well into adulthood as their song matures. We previously showed that increasing the expression of miR-9, a key brain enriched miRNA, in Area X impairs song learning and performance and alters the expression of a large number of genes important for neuronal development. These findings prompted us to examine the roles of miR-9 in regulating neuronal structure in Area X. We report that overexpression of miR-9 in juvenile Area X interferes with structural development by reducing spiny neuron dendritic arbor and spiny density in a developmental stage specific manner. We also show that miR-9 regulates the maintenance of spiny neuron structure in adulthood.Together, our results demonstrate that spiny neuron structure undergoes dynamic change during the sensitive period of song development, and miR-9 plays important roles in regulating spiny neuron structure in juveniles and in the maintenance of spiny neuron structure in adulthood.

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Poster

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This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains, Healthy Lives initiative.

Title: Developmental rearing condition differentially affects neural responses to socially relevant songs in adult female zebra finches

Authors: *I. CATALANO[1], E. M. WALL[1], S. C. WOOLLEY[2];
[1]Integrated Program in Neurosci., [2]Dept. of Biol., McGill Univ., Montreal, QC, Canada

Abstract: Communication is key to the formation and maintenance of social bonds across species. The way in which individuals respond to communication signals can be shaped by experience, including social and sensory experience, throughout the lifespan. We are interested in uncovering the neural circuits receivers use to recognize and prefer communication signals and how these are modulated by experience. In particular, previous work has found that song preferences in female zebra finches are influenced both by developmental exposure to song as well as social bonding in adulthood. We investigated the degree to which these experiences may differentially impact neural activity. In this study, we reared female zebra finches either with (normally-reared) or without (song-naïve) exposure to male song. As adults, females were co-housed with a male for two weeks, during which time they could form a pair bond. We then looked at expression of an activity-dependent marker, phosphorylated S6 (pS6), and a catecholaminergic marker, tyrosine hydroxylase (TH), which is the rate-limiting enzyme in catecholamine synthesis, in birds that heard either their mate's song, a familiar song, an unfamiliar song, or nothing (silent control). We quantified the number of cells expressing either pS6 alone or co-localized with TH in auditory processing, social behavior network, and catecholamine producing regions. We found that the inferior colliculus and caudomedial mesopallium showed increases in pS6 expression in response to song playback but did not distinguish between stimuli or rearing condition. In contrast, the caudomedial nidopallium (NCM), a secondary auditory region implicated in song learning and memory, showed rearing-dependent variation that also depended on the female's relationship to the song. Specifically, pS6-immunoreactivity (IR) in normally-reared females was greatest in response to their mate's song, while in song-naïve females, pS6-IR was higher for an unfamiliar male's song. In addition, in the ventral tegmental area (VTA), a midbrain dopaminergic region that projects to the NCM, the percentage of TH-positive neurons expressing pS6 was greater in response to the mate's song in both rearing conditions. Taken together, these data highlight how developmental song exposure and social experience differentially shape the neural responses of auditory and

dopaminergic neurons to songs that vary in social valence, and suggest that a lack of developmental song exposure may alter the processing or storage of the mate's song memory in NCM.

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Poster

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Topic: F.01. Neuroethology

Title: Gfp expression pattern in different cell types of the ubiquitin-c-gfp transgenic zebra finch model

Authors: *T. DAFALIAS[1], N. SHVEDOV[2], B. B. SCOTT[3];
[2]Grad. Program for Neurosci., [1]Boston Univ. Grad. Program For Neurosci., Boston, MA;
[3]Psychological & Brain Sci., Boston Univ., Boston, MA

Abstract: Ubiquitin - C (UBC) zebra finches have been produced using lentiviral transgenesis to express green fluorescent protein (GFP) under the human ubiquitin C promoter. These transgenic birds are previously shown to express GFP in brain tissue (Agate et al. 2009). However, it is still unclear how GFP expression varies across different cell types and brain regions. Understanding the patterns of GFP expression in the brain of this transgenic bird model is crucial for its subsequent use in future neuroscience studies. Using hybridization chain reaction fluorescent in situ hybridization (HCR-FISH) and immunofluorescence approaches, we stained for major neuronal markers and for neuronal subpopulation-specific markers in order to determine the identities of GFP-expressing cells. Here we focus on the song area HVC, as it is widely studied for its role in singing and for exhibiting robust adult neurogenesis. We first examine GFP expression in the three main HVC mature neuronal types: RA-projecting excitatory neurons (HVC_{RA}), Area X - projecting excitatory neurons (HVC_{X}), and interneurons (HVC_{INT}). We show GFP expression in more than half of HVC_{RA} neurons (60.8%, n=192/316 cells) using an HVC_{RA} specific marker (Urotensin 2B). This is in contrast to the lack of GFP expression in HVC_{X} neurons as it is determined by retrograde labeling. HVC_{INT} were identified by HCR-FISH staining for GABAergic neuron marker glutamate decarboxylase (GAD1). About half (49%, n=98/200 cells) of HVC_{INT} were GFP+. These results suggest that GFP expression might be neuron type specific, although whether variability of GFP expression within cell types is subtype-specific or otherwise determined is still unclear. Because HVC is known to exhibit robust adult neurogenesis, we also examined GFP expression beyond mature neurons in immature neuronal types. Almost half (47.5%, n=288/630) of cells expressing doublecortin (DCX), a known immature, migratory, and postmigratory neuron marker, were GFP+. Interestingly, cells expressing the previously described neural stem cell marker tenascin C (TNC) were GFP-, suggesting that GFP expression may vary throughout the different stages of

neurogenic lineage. Further experiments could examine GFP expression in more neuron subtypes, neural progenitor stages, and other non-neuronal cell types. Taken together, these findings elucidate essential parts of the identity of the cells expressing GFP in the transgenic zebra finch HVC, informing further studies into newborn cell fates and neurogenic lineage stages using this model.

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Poster

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Topic: F.01. Neuroethology

Support: NSF NRT DGE-1633516

Title: Deep brain three-photon imaging in transgenic songbirds

Authors: *N. R. SHVEDOV[1], H. E. FROSTIG[2], J. C. MERTZ[2], B. B. SCOTT[3];
[1]Grad. Program For Neurosci., [2]Col. of Engin., [3]Psychological & Brain Sci., Boston Univ., Boston, MA

Abstract: In vivo imaging has been used in songbirds to study the cellular and circuit mechanisms of local learning. In particular, two-photon microscopy (2PM) has been applied to area HVC, a dorsally located sensorimotor nucleus necessary for song production. This technique has been used to study calcium dynamics related to singing, spine dynamics related to learning, and cell migration associated with adult neurogenesis. However, 2PM is limited to the first several hundred micrometers below the brain surface, limiting researchers' ability to study biological processes deeper with HVC and in other more deeply located song nuclei. Three-photon (3P) microscopy is an emerging technology that has enabled optical access to brain depths beyond a millimeter in the rodent nervous system, and may be a useful approach to reveal biological mechanisms in deeper brain areas in songbirds. Here, we demonstrate deep brain cellular resolution imaging in the UBC-GFP transgenic songbirds using a novel 3PM system. UBC-GFP transgenic zebra finches, which express the green fluorescent protein (GFP) throughout their brains, were implanted with an optical window and a custom kinematic headplate system that enabled time-lapse imaging in awake animals. Using a custom built 3P microscope, we were able to image large populations of GFP+ cells and identify putative migratory neurons based on morphology at depths exceeding 700 microns below the surface. This exceeds the performance achieved using conventional 2PM microscopes in UBC-GFP zebra finches ~350 microns below the surface. We imaged at 1300 nm at powers of up to ~80 mW (at the sample surface) over a large field of view (2 mm). These results demonstrate the potential of 3P microscopy to study neural circuits at cellular resolution deep within the brain of songbirds.

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Poster

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Topic: F.01. Neuroethology

Support: NSERC #05016
Centre for Research in Brain, Language and Music

Title: Influence of Perineuronal Nets in Sensorimotor Circuitry on Vocal Performance

Authors: *X. WAN[1], A. S. WANG[2], J. T. SAKATA[3];
[1]Integrated Program in Neurosci., [2]Biol., McGill Univ., Montréal, QC, Canada; [3]Biol., McGill Univ., Montreal, QC, Canada

Abstract: Perineuronal nets (PNNs) are extracellular matrices that surround neurons which regulate neural dynamics and plasticity (e.g., parvalbumin (PV) neurons). The function of PNNs has been studied extensively in sensory and cognitive systems but little is known about their role in motor circuitry. The neural circuits for vocal performance and learning in songbirds ("song system") are replete with PNNs but the function of these PNNs remain unknown. We analyzed variation in the expression of PNNs in the song system of zebra finches as a function of age-dependent variation in vocal performance and investigated how degradation of PNNs affected song performance in adult zebra finches. Consistent with previous reports, PNN expression (e.g., the percent of PV neurons surrounded by PNNs) increased over development in areas like HVC, the robust nucleus of the arcopallium (RA), and the lateral magnocellular nucleus of the nidopallium (LMAN). Furthermore, PNN expression was correlated with individual variation in vocal stereotypy. To gain further insight into the contribution of PNNs to vocal performance, we examined how removing PNNs in HVC (a brain area analogous to the supplementary motor cortex) using chondroitinase ABC (ChABC) affected song performance. Compared to birds given control infusions that did not affect PNN expression (infusions of penicillinase), birds with degraded PNNs produced songs that differed from baseline song for a longer period of time. Collectively, these data suggest that PNNs influence vocal performance and could regulate neural plasticity central to vocal refinement and plasticity.

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Poster

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Topic: F.01. Neuroethology

Support: NIH Grant MH070712-09

Title: Evaluating song modification to aversive feedback following FoxP2 overexpression in adult male zebra finches

Authors: *N. DAY[1], S. FREDA[2], T. JADHAV[1], M. MCBRANCH[1], S. SURMAN[1], S. A. WHITE[3];
[1]Psychology, Whitman Col., Walla Walla, WA; [2]Northwestern Univ., Chicago, IL; [3]Integrative Biol. & Physiol., UCLA, Los Angeles, CA

Abstract: The acquisition and maintenance of complex sensorimotor skills require sensory feedback to optimize motor output. In songbirds such as male zebra finches, an essential animal model for human speech, sensorimotor learning is required throughout the lifespan to control song behavior. Juveniles imitate a tutor song during initial song acquisition whereas adults correct vocal errors during daily song maintenance. Similar to sensorimotor learning in mammals, vocal plasticity in songbirds is controlled by a basal ganglia thalamo-cortical loop. Speech impairments arising from mutations in the FOXP2 transcription factor underscore the importance of understanding how individual genes or suites of genes may influence vocal learning. Within the song-dedicated region of the avian basal ganglia, Area X, *FoxP2* is dynamically regulated based on the type and quantity of song. In juvenile zebra finches, dysregulation of *FoxP2* disrupts vocal learning. Additionally, overexpression of Area X *FoxP2* in deafened adult birds hastens song degradation, which links *FoxP2* and auditory feedback processing. To further establish a connection between *FoxP2* and sensorimotor error correction, we used disruptive auditory feedback to evoke learning in adult finches. Briefly, a bird received a short burst of white noise when he performed a specific syllable in his song above (or below) a specified pitch threshold. We hypothesize that FoxP2 overexpression will interfere with sensory-guided learning in adult birds. To test this hypothesis, we identified birds that successfully modified their song over three to five days of incremental learning. These birds were then injected with a herpes simplex virus (HSV) to drive overexpression of *FoxP2* or *GFP* (control construct) in Area X. We calculated the magnitude of change in pitch between the “Silence” and “White Noise Feedback” conditions before and after HSV injection. Preliminary data suggests that adaptive song modification is impaired following *FoxP2* overexpression, which impacts a bird’s ability to avoid an aversive stimulus. Our results implicate *FoxP2* in song evaluation, establishing a molecular basis for auditory processing that guides reinforcement-based learning.

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Poster

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Topic: F.01. Neuroethology

Support: NSF award EF-1822476

Title: The robustness of the neural mechanisms within HVC for variable syllable sequences in bengalese finch song

Authors: *A. KHARE[1], D. Z. JIN[2];
[1]The Penn State Univ., State College, PA; [2]Physics, Penn State Univ., University Park, PA

Abstract: Bengalese finch song consists of a variable sequence of syllables. Experiments and computational studies have identified the premotor brain nucleus HVC (proper name) as a key encoder for the timing of the acoustic features of birdsong [Long et al (2010)]. Further, a branch chain network within HVC was proposed as the encoder for the variable syllable sequences in Bengalese finch [Jin (2009)]. Each syllable can be encoded by a chain of excitatory neurons. Neural activity propagates down a chain, and can initiate activity in one or more chains, with support of external inputs from brain nuclei upstream of HVC. Inhibitory interneurons in HVC provide feedback inhibition, giving rise to a winner-take-all (WTA) mechanism, ensuring that only one chain gets activated. An emergent feature of this setup is the existence of a working regime, a region in the parameter space of excitation and inhibition strengths where the WTA mechanism holds. Here, we discuss the effect of incorporating temperature changes on the branch chain network. Focal cooling of HVC during singing has been identified to affect the timing [Long et al (2008)] and syntactical features of birdsong [Zhang, Wittenbach et al (2017)]. We identify that the working regime of the branch chain network under cooling has a narrow intersection with that of the network under normal conditions. Temperature changes within HVC affect excitation and inhibition strength of synapses between neurons within HVC, as well as the synapses incident on HVC neurons from other brain nuclei. Additionally, ion channel dynamics and voltage-gated conductance of neurons are also temperature dependent. We discuss how the above mechanisms affect the working regime, and further work would focus on identifying possible modifications that result in a broader intersection of the working regime of the two networks.

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Poster

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Sophomore Early Research Program fellowship

Title: Hemispheric dominance in HVC is experience-dependent in juvenile male zebra finches

Authors: J. L. HUNT, S. Y. FRANK, *S. GOBES;
Wellesley Col., Wellesley, MA

Abstract: In the human brain, left-side hemispheric dominance of the language regions is positively correlated with proficiency in linguistic skills. However, it is unclear whether this pattern depends upon language learning or is the result of pre-existing functional asymmetries. Songbirds provide a model in which we can study this question, because they learn their song in the same way that human children learn to speak, by listening to and imitating adults. Juvenile male zebra finches (*Taeniopygia guttata*) must be exposed to an adult tutor during a sensitive period in order to develop normal adult song. At the anatomical level, there are parallels as well, with pre-motor nucleus HVC playing a critical role in song learning and production (cf. Broca's area). We examined the effect of song learning on lateralization of the song system by eliminating exposure to adult vocalizations during the sensitive period. To test if the HVC exhibits hemispheric dominance prior to song learning, juvenile male zebra finches were isolated from their adult tutors at 9 days post-hatching (dph). At 57 dph, birds were exposed to a novel auditory stimulus (either song or rhythmic white noise). Stimulus-induced activity in the HVC was measured using the immediate early gene ZENK as a marker for neuronal activity. HVC lateralization was determined as the difference between Zenk-immunopositive neurons per mm2 in the right and left hemispheres, normalized by total HVC activity across both hemispheres. We found that neuronal activity in the HVC of juvenile male zebra finches is not lateralized when raised in the absence of adult song ($p > 0.05$; one sample t-test of HVC lateralization scores compared to 0), while normally-reared birds are left-dominant (Moorman et al. 2012). These findings show that there is no pre-existing functional asymmetry in the HVC prior to song exposure, suggesting that functional lateralization of the song system depends on learning through early exposure to adult song.

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Poster

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Topic:

Title: Ontogeny of Auditory Lateralization and the Effects of Developmental Experience in the Zebra Finch

Authors: *B. FUREST CATALDO[1], P. DADIKA[2], D. VICARIO[2];
[1]Psychology, Rutgers Univ., Stirling, NJ; [2]Psychology, Rutgers Univ., Piscataway, NJ

Abstract: Auditory activity in the forebrain *caudomedial nidopallium* (NCM), of the adult Zebra finch (ZF; *Taeniopygia Guttata*) is lateralized; conspecific song playback elicits larger responses in the right hemisphere than in the left, and this asymmetry is not seen in birds deprived of auditory experience as juveniles. However, the ontogeny of this response pattern, and the necessary conditions for its emergence, are unknown. The current study recorded auditory-evoked epidural potential responses bilaterally across development (40-120 days' post-hatch, phd) in male ZFs raised in three different acoustic environments: 1) a well-established tutoring paradigm where birds pecked to hear a model song (EXPLICIT); 2) a ZF aviary recording (no ZF tutor; IMPLICIT); and 3) an aviary recording from a different species, the canary (no ZF tutor; HETENV). We report that, across conditions, auditory responses were initially left-lateralized (~40-75 phd) followed by a transition to robust right-lateralization prior to and in adulthood (~80-120 phd). The age of onset of right-lateralized responses varied between exposure conditions (~60-81 phd), was earliest for EXPLICIT, but did not differ significantly between conditions. Lateralization and song development changes were positively correlated in time and, in addition, changes in auditory lateralization between successive timepoints were related to declines in a song variability metric which reflected song crystallization. Acute, bilateral, multi-unit recordings in NCM performed in the same birds in adulthood confirmed the right-lateralized pattern of activity seen in epidural responses and a condition-dependent effect on firing rates elicited by different classes of stimuli. Furthermore, multiunit responses in HETENV birds exhibited a heightened ability to decode canary exemplars relative to responses in ZFs raised in the other two conditions. These results suggest that typical right-lateralized activity in the ZF emerges during development and that juvenile experience can shape how the adult brain processes auditory stimuli.

Disclosures: B. Furest Cataldo: None. **P. Dadika:** None. **D. Vicario:** None.

Poster

PSTR090. Vocal/Social Communication—Avian I

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.20/CC8

Topic: F.01. Neuroethology

Title: Using computational tools to assess auditory processing and learning in an animal model

Authors: L. W. COLLINS[1], B. F. CATALDO[1], **M. L. PHAN**[2], S. NAKKA[1], W. LIU[1], *D. VICARIO[1];
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Abstract: Animal models are important for understanding the brain basis of sensory, neurocognitive, and social disorders, e.g. speech processing deficits, ADHD, and autism). However, current methods for assessing animal cognition are limited. The most common approach (GO-NoGO) involves training the animal to make an operant response to one sensory

stimulus and inhibit responding to another in order to test discrimination ability. Animal subjects often take many trials to learn to perform the correct behavioral response and thus cannot communicate what they already know. This can be due to the conflict between the drive to always make a response (to receive a reward) and the need to contingently inhibit a response. The GO-NoGO paradigm is also limited in the number of stimuli that can be tested. To address these limitations, we have advanced a method to test discrimination between acoustic stimuli that uses machine learning (ML) to quantify a natural orienting behavior, head turning, in adult zebra finches (ZFs), a well-established model system for studying the brain basis of vocal communication, with many parallels to speech processing. We measured micro-movements that ZFs make with their heads when a different stimulus (oddball) is unexpectedly played in a sequence of repeating stimuli (standards), violating expectations. Available ML algorithms, e.g. DeepLabCut, were trained to track landmarks on the bird's head in video recordings made during stimulus playbacks. The oddball stimuli evoked a distinct pattern of short latency head movements that demonstrated the birds' ability to distinguish between the two sounds. Auditory discrimination was assessed by varying acoustic differences between the standard and oddball stimuli, typically ZF or canary songs. Multiple stimulus pairs can be tested in a few hours, a process that would have taken weeks using the GO-NoGO method. This novel head tracking approach has the potential to replace time-consuming conditioning methods (days-weeks; task learning/shaping required) with a more efficient way (20min; no task learning/shaping required) of assessing what ZFs can hear and relating their abilities to stimulus characteristics, memory processes, and neural activity.

Disclosures: L.W. Collins: None. **B.F. Cataldo:** None. **M.L. Phan:** None. **S. Nakka:** None. **W. Liu:** None. **D. Vicario:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.01/CC9

Topic: F.03. Stress and the Brain

Support: VA Grant BX005923

Title: Traumatic stress-induced glucocorticoid signaling and rat behavior

Authors: *E. DEVINE[1], J. B. CHAMBERS[2], M. A. SMAIL[3], J. P. HERMAN[4];
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[2]Pharmacol. & Systems Physiol., [3]Univ. of Cincinnati, Univ. of Cincinnati, Independence, KY;
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Abstract: It is estimated that 3.6% of the world population is affected by post-traumatic stress disorder (PTSD), creating a massive economic burden. Experiencing severe or traumatic stress impacts the brain by altering emotional processing, leading to hyperarousal, expressed as

increased anxiety, hypervigilance, and deficits in impulse control and fear memory extinction. This hyperarousal is thought to occur via dysfunctional glucocorticoid receptor (GR) signaling upon exposure to trauma. Previously, we found increased plasma corticosterone (CORT) in male rats 24 hours post- exposure to a single-prolonged stress (SPS) exposure relative to unstressed controls. SPS is used as a method to recapitulate PTSD-related behaviors in rats. Using this method, we previously described enhanced threat assessment behaviors in rats in an open field test, impaired novel object discrimination and increased threat avoidance in rats previously exposed to SPS. Other studies indicate that administration of GR antagonists after SPS exposure block SPS-induced deficits in extinction of fear memory. Given these data, we hypothesize that GR signaling drives the development of behavioral pathologies associated with SPS.To test this hypothesis, male rats received bilateral implantation of cannulas into the infralimbic cortex (IL), a brain region important for fear memory extinction and emotional regulation. Two weeks after implantation, rats were either briefly removed from their home cage (control) or exposed to SPS. All rats then immediately received infusion of either vehicle or mifepristone, a GR antagonist, and received additional doses for the two days following. One week later, rats completed fear/anxiety-related behavioral testing, including open field, novel object, elevated plus maze, and passive avoidance. Data are currently being analyzed by factorial or repeated measures designs as appropriate.

Disclosures: **E. Devine:** None. **J.B. Chambers:** None. **M.A. Smail:** None. **J.P. Herman:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.02/CC10

Topic: F.03. Stress and the Brain

Support: NIMH Grant K08 MH122733
United States Department of Defense
VA National Center for PTSD

Title: Corticotrophin releasing factor dynamics in learned and innate threats

Authors: *J. COOK[1], A. BASU[2], S. STASZKO[2], J.-H. YANG[2], Y. LI[3], A. P. KAYE[2];
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Abstract: Traumatic experiences can lead to long-lasting alterations in stress-related brain regions, including the medial prefrontal cortex (mPFC), locus coeruleus, paraventricular hypothalamus (PVH), and bed nucleus of the stria terminalis (BNST). Dysregulation of the neuropeptide corticotrophin-releasing factor (CRF) has been implicated in trauma-related disorder, including by genome-wide association studies have implicating CRF receptor 1 (CRFR1) in risk for posttraumatic stress disorder. In order to understand the role of CRF in

stress-related threat processing, we sought to identify a role for CRF in stress-sensitized moment-to-moment threat processing. To address this gap, we used computational behavior tracking, pharmacology, and neuropeptide sensor techniques in the stress-enhanced fear learning (SEFL) model of PTSD. Our results revealed that administration of a selective CRFR1 antagonist (antalarmin) blocked the stress sensitization of contextual fear learning in the SEFL model. Furthermore, computational behavior tracking (MoSeq) unveiled distinct stress-related behavioral states that were also altered by the CRFR1 antagonist. To gain deeper insights into CRF dynamics during stress sensitization, we used fiber photometry of GRAB sensors (GRAB-CRF3.0) to measure CRF release in response to learned and innate fear stimuli. Validation experiments demonstrated CRF release in the mPFC in response to diverse threatening stimuli. Subsequently, we conducted GRAB-CRF3.0 recordings during the SEFL behavioral paradigm. We will also utilize two-photon imaging and optogenetic perturbation to clarify distinct functions of CRF release in the context of learned and innate threat processing. By delineating neuropeptide dynamics in threat-related behaviors, our findings shed light on the potential of CRFR1 antagonism in attenuating the effects of SEFL following prior exposure to traumatic stressors.

Disclosures: **J. Cook:** None. **A. Basu:** None. **S. Staszko:** None. **J. Yang:** None. **Y. Li:** None. **A.P. Kaye:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.03/CC11

Topic: F.03. Stress and the Brain

Title: Corticosterone administration in adolescence enhances habit learning and impairs cognitive learning in adult rats

Authors: *T. M. GADBERRY, M. G. PACKARD;
Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: The mammalian brain consists of multiple memory systems, including a hippocampal-dependent cognitive memory system and a habit memory system mediated by the dorsolateral striatum (DLS). *Early-life stress* (ELS) in humans is associated with a predisposition to psychopathologies both characterized by *maladaptive habitual behaviors* (e.g., OCD, PTSD, SUD) and attributed, in part, to altered memory system function. Stress tends to impair hippocampal cognitive memory while enhancing DLS habit memory in adults, yet these effects have not been extensively investigated in the context of ELS, particularly within adolescence. We previously observed that repeated systemic administration of the primary stress hormone corticosterone (CORT) in adolescent rats induced a subsequent *enhancement* of DLS-dependent habit formation in a *response learning* water plus-maze task in adulthood, and the effect was *blocked* by concurrent administration of the glucocorticoid receptor antagonist Mifepristone

(MIFP). The present experiment investigated the effects of chronic CORT administration in adolescence on *hippocampus-dependent place learning* in the plus-maze as adults. Long-Evans male adolescent rats (PND $37^{\pm 4}$) received a single peripheral injection of either CORT (5-mg/kg) or its vehicle for five days. All subjects were then allowed to mature into adulthood (PND 60+) before behavioral testing commenced in a hippocampus-dependent place learning task. In this task, rats are released from different starting arms (N, S) of a submerged plus maze and trained to swim to a fixed spatial location (W) to mount a hidden escape platform. Relative to controls, rats chronically administered CORT during adolescence were *impaired* in place learning as adults. Taken together, the effects of adolescent CORT administration on *response* and *place learning* tasks as adults mimic the effects observed following *hippocampal damage* in adulthood (i.e., an enhancement of response learning and impairment of place learning). Thus, ELS could influence the use of different memory systems in adulthood, in part, by impairing hippocampal development/function via chronic glucocorticoid receptor activation. Further, the parallel enhancement of adult habit memory following ELS may predispose individuals to the development and/or expression of maladaptive habitual behaviors associated with various psychopathologies.

Disclosures: T.M. Gadberry: None. **M.G. Packard:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.04/CC12

Topic: F.03. Stress and the Brain

Support: The Saban Research Institute Predoctoral Award
NIH R01-MH120133
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Canadian Institute for Advanced Research
Developmental Neuroscience & Neurogenetics Program, TSRI, CHLA

Title: Intergenerational legacies of paternal glucocorticoid exposure

Authors: *W. W. TAYLOR[1,2], W. Y. LIU[2], L. KOROBKOVA[1,2], L. VASQUEZ[1,2], S. STACK[1,2], N. BHINDERWALA[2], V. GAO[2], E. MORALES[2], R. AHMED[2], B. G. DIAS[2,3]; [1]USC, Los Angeles, CA; [2]Div. of Endocrinol., Children's Hosp. Los Angeles, The Saban Res. Inst., Los Angeles, CA; [3]Pediatrics, Keck Sch. of Medicine, USC, Los Angeles, CA

Abstract: Recently, there has been interest in understanding the influence of maternal glucocorticoid exposure during pregnancy on subsequent physiology and behavior of the offspring. With glucocorticoids also being prescribed to males, missing from this perspective is any potential legacy that paternal glucocorticoid exposure may have on progeny conceived in the shadow of glucocorticoid exposure. To address this, we investigated how corticosterone (CORT)

exposure in paternal F0 male mice impacts cognitive, affective, and social behavior in the F0 and F1 generations. In addition to behavioral legacies, we explored how paternal CORT shapes neurobiology and endocrine function within and across generations. To address this, adult male mice were given access to 25 ug/ml of CORT via drinking water for 14 days followed by 12.5 ug/ml CORT for 3 days, 6.25 ug/ml CORT for 3 days, and finally standard water. The Control (CTRL) group was given standard water throughout. One week later, F0 males were used for endocrine studies, neurobiological analyses, and behavioral testing. Independent groups of F0 CORT or F0 CTRLs were mated with naïve females to generate F1 CORT and F1 CTRL cohorts. For neurobiological and endocrine measures, CORT and CTRL mice were sacrificed following a single restraint stress and blood plasma and brain region punches were collected. Cognitive behavior was assayed via auditory fear conditioning, extinction training, and extinction recall. Affective and social behavior was assayed using the open field and social interaction tests. F0 CORT mice showed deficits in extinction learning and in extinction recall compared to F0 CTRL mice, as measured by heightened freezing during extinction and extinction recall. Anxiety-like behavior as measured by the open field test was not different between the F0 CORT and F0 CTRL mice. However, F0 CORT mice spent more time avoiding interaction with a female conspecific in the social interaction test. Male, but not female, F1 CORT offspring showed enhanced recall of fear conditioning and trended towards deficits in extinction recall compared to F1 CTRLs. Male F1 CORT offspring showed heightened anxiety-like behavior while female F1 CORT trended towards expressing less anxiety in the open field test. Our results not only suggest that glucocorticoids influence behavior in directly exposed males but also that paternal exposure to glucocorticoids bequeaths a sexually dimorphic legacy on cognitive, affective, and social behavior in offspring. Furthermore, positive results from our neurobiological and endocrine analyses stand to illuminate how a legacy of glucocorticoid exposure shapes biology within and across generations.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.05/CC13

Topic: F.03. Stress and the Brain

Support: RO1-MH115049
RO1-MH115914

Title: Exploring the impact of early life adversity on stress-enhanced fear learning and drug seeking

Authors: *B. L. WILLIAMS[1], K. G. BATH[2];
[1]Cell. and Mol. Physiol. & Biophysics, Columbia Univ., New York, NY; [2]Developmental Neurosci., New York State Psychiatric Inst., New York, NY

Abstract: Stress is a major risk factor in the development of addiction and relapse susceptibility. Prior work has shown that multiple stressors across the lifespan can have compounding effects on the risk for pathology. However, the mechanisms by which stressors contribute to this increased vulnerability are still poorly understood. Here, we tested the impact of early life adversity (ELA) and exposure to a secondary stressor later in life, stress enhanced fear learning (SEFL), on risk for behaviors implicated in maladaptive stress responding, including fear generalization and drug seeking. The corticotropin-releasing hormone (CRH) system is particularly sensitive to stress and has been implicated in addiction and stress-induced relapse. Specifically, the central amygdala (CeA), a key site of CRH activity and regulation, has been shown to mediate the expression of fear and the incubation of drug craving. Projections from the CeA to the nucleus accumbens (NAc) have also been shown to modulate reward-related behaviors in a CRH-dependent manner. Additionally, CRH microinjections into the NAc lead to positive conditioned place preference (CPP) and increased NAc dopamine (DA) release in mice. ELA, or significant stress later in life, has been shown to alter the expression of Crh-associated genes in CeA. However, the combined effects of a double hit of stress (such as ELA and SEFL) on the CRH system has not been explored thus far. In response to ELA and SEFL, we found that ELA reared animals showed reduced freezing to an unconditioned tone in a novel context following SEFL, compared to controls that did not undergo ELA. We also observed sex-specific and rearing-selective effects on fear extinction. These results demonstrate that ELA contributes to underlying differences in fear expression circuitry. In ongoing work, activity of CRH+ CeA neurons are being measured in response to stress and in the context of stress-induced drug relapse. The results of this work will contribute to our understanding of the interaction of the effects of ELA and secondary stressors on stress-susceptible fear and reward circuitry and have the potential to inform the development of circuit specific treatments and interventions that are informed by prior experience.

Disclosures: B.L. Williams: None. **K.G. Bath:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.06/CC14

Topic: F.03. Stress and the Brain

Title: Effect of Iterative stressful stimuli on defensive burying in rats: Effect of diazepam and fluoxetine.

Authors: *A. J. SALDIVAR-GONZALEZ[1], M. MARTINEZ-ROMERO[2], E. PEREZ SEPULVEDA[2];

[1]Pharmacol., Univ. Nacional Autonoma De Mexico, México, Mexico; [2]Pharmacol., Natl. Autonomous Univ. of Mexico, Mexico City, Mexico

Abstract: Effect of Iterative stressful stimuli on defensive burying in rats: Effect of diazepam and fluoxetine. J.A Saldívar-González, M. Martínez-Romero, E.M. Perez-Sepúlveda. Department of Pharmacology. Faculty of Medicine. National Autonomous University of Mexico. In regular conditions the individuals are exposed to a constant flow of different kind of stimuli. Therefore, iterative stimuli in rats have been studied. Defensive burying model developed for the screening of putative antianxiety agents, has demonstrated to be a useful tool for studying emotional responses. The participation of GABA and Serotonin systems in mediating anxiety responses has been also reported. Thus, diazepam (Dz), a benzodiazepine receptor agonist of the $GABA_A$ receptor complex and fluoxetine an inhibitor of serotonin reuptake transporter has been used widely in rats' anxiety models. With the aim to analyze the effect of Dz and Fluox in mediating behavioral changes elicited by repeated electric stimuli in DB model the present work was carried out. Wistar male rats, 250-300 gr were used. Through the experiments the individuals were maintained in an inverted, 12 hrs light- dark cycle, with an ad libitum access to food and water. Defensive burying elicited after touching the electrode (0.5 mA) was recorded and expressed in sec, after ten minutes elapsed. A number of electrode touches and the height that reached the covering cage material (clean sawdust) were also recorded. Both Dz and Fluox were administered orally, diluted in the water of drinking bottle, a volume replaced each 24 hrs for a new fresh and adjusted drug concentration depending to a previous consumption day. Control subjects, non-stimulated, were treated with Dz (0, 1.0, 3.0 and 5 mg/kg) for five consecutive days. Another group was treated with Fluox (10, 20 and 30 mg/kg) for ten consecutive days. The experimental group received a single 0.7 mA shock 90 sec before DB test. The subjects received Dz or Fluox as mentioned above. The data were analyzed by a Kruskal Wallis ANOVA followed by the Mann Whitney U test. The electric shock delivered 90 sec before DB test, elicited a remarkable increase in defensive burying. Both Dz and Fluox decreased burying behavior in a dose dependent manner in the two experimental groups. Nevertheless, a most robust reduction in DB in previously shocked groups can be observed. The results are discussed in terms of the putative differential sensitivity of GABA and serotonergic systems elicited by iterative stressful stimuli in rats.

Disclosures: A.J. Saldivar-Gonzalez: None. **M. Martinez-Romero:** None. **E. Perez Sepulveda:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.07/CC15

Topic: F.03. Stress and the Brain

Support: NIMH R01 MH122712
NIMH R01 MH122712S1

Title: Properties of VTA Nos1 GABAergic neurons and their contributions to stress responses

Authors: *K. M. PRICE[1,2], D. TORTOZA[2], E. APPEL- CARACCIOLI[2], M. WYNALDA[2], A. M. POLTER[2];
[1]Pharmacol. and Physiol., The George Washington Univ., Arlington, VA; [2]Pharmacol. and Physiol., George Washington Univ., Washington, DC

Abstract: The ventral tegmental area (VTA) is well characterized for its dopaminergic projections to targets in the mesocorticolimbic system contributing to aversion, reward- related and motivated behaviors, and stress responses. GABAergic neurons in the VTA are known to robustly inhibit firing of VTA dopamine neurons, but their specific contribution to the functional heterogeneity of the VTA is not well understood. GABAergic neurons in the VTA make both local connections and distal projections. Given that morphological, physiological, and molecular criteria for classification of forebrain inhibitory interneurons are unreliable for the VTA, there were no previous molecular markers to distinguish inhibitory interneurons from projection neurons in the VTA. However, recent work (Paul et al., *eNeuro* 2018) demonstrated that neuronal nitric oxide synthase (Nos1) is a marker for a subset of VTA GABAergic neurons that do not project out of the VTA and do not express tyrosine hydroxylase, indicating that they are likely inhibitory interneurons. In order to probe properties of VTA Nos1 synapses, we injected a Cre- dependent channelrhodopsin adeno-associated virus into the lateral VTA of Nos1-Cre mice and recorded optically- evoked currents and firing rates in VTA dopaminergic neurons. Our preliminary data revealed both putative excitatory (currents evoked at -70 mV, -52.26 ± 6.776 pA) and putative inhibitory (currents evoked at 0 mV, 57.76 ± 29.37 pA) Nos inputs on VTA DA neurons, which is consistent with prior evidence showing that a population of Nos- expressing neurons in the VTA are glutamatergic. We then subjected male and female Nos-tdTomato mice to acute tail suspension stress and measured C-Fos expression as a proxy for neuronal activation to examine a role of VTA Nos1 neurons during stress. Our results suggest that VTA DA neurons receive input from local VTA Nos1 neurons. Further experiments to examine the synaptic properties and activity of VTA Nos1 neurons during stress and reward will be instrumental in revealing architecture of VTA microcircuitry and its contribution to stress- induced changes in reward processing.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR091.08/CC16

Topic: F.03. Stress and the Brain

Support: NIH Grant R00 MH106757
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Young Investigator award from the Brain and Behavior Research Foundation
Research grant from the Margaret Q. Landenberger Foundation

Title: Subchronic stress elicits sex-specific changes in VTA dopaminergic circuitry

Authors: *M. WYNALDA, C. BOUARAB, A. KISNER, A. M. POLTER;
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Abstract: Subchronic stress elicits sex-specific changes in VTA dopaminergic circuitry

Megan M. Wynalda[1], Chloé Bouarab[1], Alexandre Kisner[1] Abigail M. Polter[1]
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Depression is a highly prevalent stress-linked disorder that is diagnosed roughly twice as often in females as males. Given that depression is a stress-linked disorder, investigating sex differences in stress responses could provide insight into female-specific vulnerability to MDD and other stress-related illnesses. Dysregulation of the mesolimbic pathway has been shown to play a role in the pathophysiology of stress-related illnesses. The ventral tegmental area (VTA) is well known for its critical role in reward and aversion. Dopaminergic neurons within the VTA are strongly regulated by both local and distal inputs and play an important role in encoding and regulating rewarding stimuli. This circuitry is highly responsive to stress and is an essential substrate for expression of stress-induced behavioral alterations in reward seeking, social, and approach-avoidance behavior.

Subchronic variable stress (SCVS) is a behavioral paradigm that models the increased vulnerability of female mice to anhedonia and anxiety following stress. In this study, we used SCVS to examine sex differences in regulation of VTA circuitry by stress. Using slice electrophysiology, we found that the firing rate of dopaminergic neurons was decreased in female, but not male mice. Surprisingly, we found an increase in inhibitory tone onto dopaminergic neurons and an increase in the firing rate of VTA GABAergic neurons in both male and female mice following SCVS. In male mice however, SCVS induced a robust upregulation of glutamatergic tone onto dopaminergic, suggesting a compensatory mechanism that is protective against diminished dopaminergic tone. In our ongoing studies, we are using fiber photometry of the dopaminergic biosensor dLight to measure spontaneous and reward-evoked dopaminergic responses in the nucleus accumbens before and after SCVS.

Through these studies, we hope to elucidate the mechanisms of sexually divergent regulatory changes in the VTA in response to stress. We have shown that there is both shared and sex-specific remodeling of VTA circuitry in males and females following SCVS. Our ongoing studies will reveal how this remodeling impacts dopaminergic responses in behavior animals. Understanding of these mechanisms creates opportunities for the development of sex-specific treatments for stress-linked disorders.

Disclosures: M. Wynalda: None. **C. Bouarab:** None. **A. Kisner:** None. **A.M. Polter:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.09/CC17

Topic: F.03. Stress and the Brain

Title: Genetic loss of the dopamine transporter impacts a subset of stress-induced alterations in behavior and signal transduction in mice

Authors: *B. SACHS, A. PETRI, A. SULLIVAN, K. ALLEN;
Villanova Univ., Villanova, PA

Abstract: The dopamine transporter (DAT) is a major regulator of dopaminergic neurotransmission, which is known to play a critical role in stress susceptibility. However, the impact of genetic loss of DAT on stress responses has not been extensively studied. The current work compared the effects of the five-day-stress (5DS) model of sub-chronic stress on animal behavior and signal transduction in the nucleus accumbens (NAc) of male and female wild-type (WT) and DAT knockout (KO) mice. Using a panel of behavioral assays, including the light-dark emergence test, the forced swim test, the elevated plus maze, and the splash test of grooming behavior, our results reveal that DAT-KO mice exhibit behavioral alterations both at baseline and following stress. In general, DAT-KO mice appeared to be less sensitive to stress-induced behavioral alterations. This was particularly evident in the light-dark emergence test, where a genotype by stress interaction was observed in which 5DS increased latency to enter the light chamber in WT mice, but not in KO animals. No sex by stress by genotype interactions were observed by three-way ANOVA for any of the behavioral tests. However, consistent with our prior work in c57BL6 animals, male mice were more susceptible to stress-induced increases in immobility in the forced swim test compared to females, regardless of genotype. A trend towards a sex by stress interaction was also observed in the splash test of grooming behavior, in which stress tended to increase grooming time in females and decrease it in males, but this trend was mostly apparent in WT mice, not DAT-KOs. In addition to these behavioral changes, DAT-KO mice were shown to exhibit increased NAc expression of deltaFosB and ERK, two signaling molecules that have been previously implicated in stress susceptibility. A significant stress by genotype interaction was observed for GSK3β phosphorylation in the NAc in which no genotype differences in pGSK3 levels were observed at baseline, but DAT-KO mice had less pGSK3 than WT animals following stress. Overall, these results provide further evidence of the importance of dopaminergic neurotransmission in determining stress responses and suggest that genetic loss of DAT can confer partial resilience to stress-induced increases in anxiety-like behavior.

Disclosures: **B. Sachs:** None. **A. Petri:** None. **A. Sullivan:** None. **K. Allen:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.10/CC18

Topic: F.03. Stress and the Brain

Support: NIMH Grant MH097988

Title: Pac1 receptor antagonism in the medial habenula rescues anhedonic effect of chronic stress in rats

Authors: *N. R. FONTAINE[1], M. AKTAR[1], W. BLACK[1], A. MAHLER[1], V. MAY[2], S. E. HAMMACK[1];
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Abstract: Previously, we have demonstrated that the activation of the central pituitary adenylate cyclase activating polypeptide (PACAP) systems plays a crucial role in mediating the effects of exposure to stressors. Additionally, chronic stress leads to a significant increase in PACAP expression in the bed nucleus of the stria terminalis (BNST). We have argued that this increase is vital for the behavioral and physiological consequences resulting from exposure to stressors. By using PACAP-ires-Cre mice with Cre-dependent reporter expression, we have identified a PACAP projection from the BNST to the medial habenula (MHb) and have also confirmed the presence of PAC1 receptors in MHb neurons. Anhedonia, which refers to the inability to experience pleasure from typically enjoyable activities, is a common symptom of depression. It is also a behavioral consequence of chronic stress in rodents and may be influenced by MHb function. We have previously shown PACAP infusions to the MHb to be sufficient to induce anhedonia as measured by the sucrose preference test—and that such behavior is PAC1-dependent. Here we investigated whether PACAP antagonism would block the effects of chronic stress. To do so, male rats were subjected to a two-week chronic variate stress paradigm and received bilateral MHb infusions of PAC1 antagonist PACAP(6-38) prior to sucrose preference testing. We found that PAC1 antagonism rescued the anhedonic effects of stress and restored sucrose preference to levels comparable those in no-stress controls. This, along with our previous findings, suggests that the binding of PACAP to PAC1 receptors in the MHb is both necessary and sufficient to induce anhedonia in male rats.

Disclosures: **N.R. Fontaine:** None. **M. Aktar:** None. **W. Black:** None. **A. Mahler:** None. **V. May:** None. **S.E. Hammack:** None.

Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.11/CC19

Topic: F.03. Stress and the Brain

Support: NIH grant R01 MH119814

Title: Effects of CNO dosage on chemogenetic activation of PL-BLA projection neurons

Authors: C. FOLTZ, D. BUESING, J. CHAMBERS, U. ANJUM, J. HERMAN, J. ZHAN, *Y. ULRICH-LAI;
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Abstract: Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are genetically modified receptors widely utilized in neuroscience research to precisely manipulate neural circuits. Clozapine-N-Oxide (CNO) is a commonly used ligand that activates DREADDs in a dose-dependent manner. With excitatory DREADDs however, standard doses of CNO generally provide maximal circuit activation, making it difficult to detect how prior experimental manipulations (e.g., chronic stress) may potentiate circuit activation. Therefore, we tested various CNO doses to determine a sub-maximal one for activating prelimbic (PL) prefrontal cortex (PFC) projections to the basolateral amygdala (BLA), a pathway implicated in anxiety-related behaviors. Adult male Long-Evans rats received bilateral infusions of a retrograde Cre-encoding virus (rAAV-hSyn-HI-eGFP-Cre) in the BLA and a Cre-dependent DREADD-encoding virus (AAV2-hSyn-DIO-hM3D(Gq)-mCherry) in the PL. Four, five, and six weeks after surgery, rats underwent social interaction (SI), novel object interaction (NOI), and elevated plus-maze (EPM) assays, respectively. Rats received an i.p. injection of 0, 0.3, 1, or 3 mg/kg of CNO 30 minutes prior to testing. Brains were collected for immunolabeling after the EPM assay. cFos expression in DREADD-infected neurons increased significantly with CNO dose (one-way ANOVA, $p<0.001$), with a sub-maximal response at 0.3 mg/kg. In the NOI test, rats exhibited a dose-dependent reduction in the total distance traveled (one-way ANOVA, $p=0.024$), center entries (one-way ANOVA, $p=0.024$), and duration spent in the center of the arena (one-way ANOVA, $p=0.054$), while no effects were observed in the EPM and SI assays. Notably, a small amount of virus expression spread into adjacent PFC regions that often provide opposing effects on stress regulation, complicating data interpretation. To address this, we are implementing machine learning models to relate PFC activation to BLA neuron activation and behavioral endpoints. Preliminary correlation analyses indicate CNO dose can be accurately predicted given the proportion of activated mCherry neurons in the PL (Pearson correlation, $r(114) = 0.39$, $p<0.001$). Additionally, total cFos expression in the BLA tends to be the best predictor of time spent in the periphery during the NOI test (one-way ANOVA, $p=0.0517$). Although analysis is ongoing, these results highlight a submaximal CNO dose suitable for future experiments using Gq DREADDs, provide insight into the role of PL-BLA projections in anxiety-related behaviors, and will establish unique computational methods for complex chemogenetic analyses.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.12/CC20

Topic: F.03. Stress and the Brain

Support: Fondecyt 1231012
Fondecyt 1201848

Title: Role of the excitatory amino acid transporter EAAT3 in resilience to chronic stress

Authors: *N. M. ARDILES[1,2], V. T. TAPIA[1,2], N. BAEZA[1,2], A. E. CHÁVEZ[2,3], P. R. MOYA[1,2];
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Abstract: The pathophysiology of depression is associated with impaired glutamate uptake and dopaminergic transmission in brain regions mediating cognitive-emotional behaviors. The excitatory amino acid transporter 3 (EAAT3) plays an important role in neuronal glutamate uptake providing a fine-tuning transmission and protecting against excitotoxicity. This study aims to determine, at a behavioral and molecular level, if the increased expression of EAAT3 in the forebrain of mice (EAAT3^{glo}/CaMKII) can counteract susceptibility to chronic stress. Our results indicate that EAAT3^{glo}/CaMKII mice subjected to unpredictable mild chronic stress (UCMS) did not show a decrease in sucrose consumption nor an increase in immobility time in the tail suspension test. Moreover, stressed EAAT3^{glo}/CaMKII mice did not show deficits in memory tasks nor in sociability when compared to stressed control littermates (EAAT3^{glo}). At molecular levels, we found that UCMS increased the levels of NMDA receptor subunit GluN2B and decreased the levels of EAAT1 and GluN2A subunit in the ventral hippocampus of stressed EAAT3^{glo} mice compared to stressed EAAT3^{glo}/CaMKII mice. Interestingly, unlike EAAT3^{glo} mice, UCMS did not impair dopamine release triggered by phasic stimulation in the nucleus accumbens shell of EAAT3^{glo}/CaMKII mice. Altogether, our results suggest that forebrain EAAT3 overexpression may be linked to a resilient phenotype to chronic stress, highlighting the relevance of this model for translational studies of mechanisms and biomarkers of resilience to stress.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.13/DD1

Topic: F.03. Stress and the Brain

Support: ICMR (SRF) F. No. 45/22/2022-PHA/BMS
SERB-CRG/2020/004971

Title: Modulation of the medial prefrontal cortex serotonergic system with deep brain stimulation of LH-MFB reversed the depression-associated cognitive deficit

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Abstract: Chronic depression is a disabling condition associated with cognitive deficits. Depression induced by chronic stress exposure results in neurochemical alterations including 5-HT and aberrant reward processing. Long-term use of antidepressants fails to improve the health of depressed patients because of treatment-resistant depression (TRD). Deep brain stimulation (DBS) of lateral hypothalamus-medial forebrain bundles (LH-MFB) is an effective therapeutic approach used for the treatment of severe depression, however, the underlying mechanisms are still enigmatic. The goal of the current study is to investigate the mechanism of LH-MFB DBS responsible for the antidepressant effect in chronic unpredictable mild stress (CUMS) induced depressed rats. Adult male Wistar rats were exposed to CUMS for 42 days and depressive behavior was assessed. The CUMS rats showed increased immobility time in the forced swim test (FST) and anxiety in the home-cage emergence test (HCET). However, a decrease in sucrose consumption in the sucrose consumption test (SCT) and memory deficits in the novel object recognition test (NOR) was observed. CUMS leads to a reduction in body weight, 5-HT and 5-HIAA levels in the medial prefrontal cortex (mPFC). Moreover, dendritic arbors and length were significantly decreased in the neurons of layers II/III and V/VI of the mPFC. The blood corticosterone level in CUMS rats was increased, whereas degeneration of 5-HT cells in the dorsal raphe nucleus (DRN) was noticed. Interestingly, DBS of LH-MFB recovered the animals from anhedonia, behavioral despair, memory deficit, anxiety, and also improved body weight. In addition, mPFC 5-HT and 5-HIAA levels, dendritic arbors of mPFC neurons of layer I/III and V/VI were dramatically increased in CUMS+ DBS rats. The elevated level of blood corticosterone significantly changes to the normal level and also prevents the loss of DRN 5-HT cells after DBS treatment in CUMS rats. The results suggest that the DBS targeted at LH-MFB may amplify 5-HT action in mPFC by modulating 5-HT innervations originating from DRN and alleviating depressive behavior and cognitive deficits in rats.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.14/DD2

Topic: F.03. Stress and the Brain

Title: Sex-dependent differences in intra-hippocampal and hippocampal-prefrontal coherence in a mouse model of adolescent social instability stress

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Abstract: Early life stress (ELS) can dramatically alter an individual's life trajectory. For example, childhood trauma, neglect or poverty is associated with later-life cognitive dysfunction and the development of adult psychiatric outcomes such as depression, anxiety, schizophrenia, and substance abuse. Importantly, the impact of ELS on life trajectory depends on the developmental phase in which stress is encountered (infancy vs. childhood vs. adolescence). Animal studies that utilize stressors during pre-weaning phases of development, such as maternal separation, neonatal isolation, limited bedding and nesting, and handling have revealed critical links between ELS and deficits in hippocampal-dependent memory function. Yet, comparable studies to determine the relationship between adolescent stress and the emergence of late-life cognitive impairments and/or neural network dynamics are lacking. In this study we characterize the effects of chronic adolescent social instability stress (SIS) on intra-hippocampal (CA3-dorsal CA1) and hippocampal-prefrontal (ventral CA1-mPFC) circuits in male and female mice. We recorded local field potentials from 17 control and 19 social instability mice, across two time points, including one proximal to stress (2 weeks post-stress) and one distal (6 months post-stress). Animals were evaluated for episodic memory (novel object recognition), social affiliation (social interaction), and anxiety (elevated plus maze). We found that female SIS animals at the late timepoint showed signs of reduced anxiety, spending more time in the open arms of the plus maze and female mice overall showed a reduced preference for social interaction. These observations were accompanied by sex-dependent differences in intra-hippocampal and hippocampal-prefrontal coherence measures. Together, these results (1) indicate an important mediating role of sex in the effect of adolescent stress on later-life anxiety and (2) suggests male and female mice may utilize different hippocampal and hippocampal-prefrontal pathways during memory-guided behavior.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR091.15/DD3

Topic: F.03. Stress and the Brain

Support: NIH Grant 4R00MH117271-03

Title: Cognitive, Neurophysiological, and Stress-Related Differences in Prolonged vs. Self-Initiated Head Restraint

Authors: *M. H. CRISTINO[1], J. RYBCZYK[1], M. PREIBISZ-KAMAT[1], T. SPELLMAN[2]; [1]Univ. of Connecticut, Storrs, CT; [2]Neurosci., Univ. of Connecticut, Farmington, Farmington, CT

Abstract: Chronic stress has been shown to affect synaptic plasticity and excitability in prefrontal neurons and has been shown to disrupt attentional set-shifting - a test of cognitive flexibility that depends on prefrontal cortex (PFC) activity. A significant obstacle to studying the effects of chronic stress in head-restrained mice is that prolonged head restraint, necessary for many types of chronic in vivo neural recording, itself induces stress. We examined whether mice performing a self-initiated head restraint (SIHR) task would exhibit differences in stress-related, cognitive, and neurophysiological measures compared with mice undergoing more standard prolonged head restraint tasks (control group). For SIHR mice, our existing behavioral apparatus, previously developed and validated for use with an attentional set-shifting task, was altered, using schematics and components from a recently published methods paper for the design of a voluntary head restraint system. This design was further altered to allow for simultaneous in vivo microscopy. Materials for replicating the behavioral setup (custom circuit board, 3D printed hardware models, full parts list, and Arduino code) are to be made accessible through open access. 10 male C57BL/6J mice were water restricted, with 5 mice designated for SIHR and 5 designated for standard prolonged head restraint during habituation, shaping, and training on a somatosensory discrimination task. Stress was monitored via corticosterone concentrations in tail-blood samples using ENZO's corticosterone ELISA kit. In initial testing, SIHR mice (N=5) took an average of 1903 +/- 233 trials to acquire shaping (consistent whisker cue-induced licking) and simple discrimination (SD) behavior, while control mice (N=5) took an average of 1281 +/- 498 trials. For corticosterone concentrations, a baseline ELISA test was performed before training to determine the average resting corticosterone levels in all 10 mice (mean = 90 +/- 77 ng/dL). In blood samples taken immediately after the successful acquisition of SD, corticosterone concentration in SIHR mice (N=5, 369 +/- 152 ng/dL, 3.611 z-scores from baseline) was higher than in control mice (N=5, 552 +/- 214 ng/dL, 6.3 z-scores from baseline). While SIHR mice exhibited slower task shaping and learning than control mice, blood plasma tests of corticosterone concentration indicate reduced stress in SIHR mice. This result provides a potential neuroendocrinological basis for adopting the SIHR platform for studying the effects of chronic stress on prefrontal activity and attentional set-shifting.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

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Program #/Poster #: PSTR091.16/DD4

Topic: F.03. Stress and the Brain

Support: NIH grant R01 MH119814 (YMU/JPH)

Title: Casting a net on stress: the effect of stress-relieving food reward on the perineuronal nets of parvalbumin interneurons in the basolateral amygdala

Authors: *H. NASHAWI[1,2,3], C. T. FOLTZ[1,3], M. A. SMAIL[1,2,3], C. PHARES[1,3], D. R. BUESING[1,3], J. P. HERMAN[1,3], Y. M. ULRICH-LAI[1,3];
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Abstract: Chronic stress has detrimental effects on both physical and mental health. Engaging in rewarding activities on a regular basis can help build resilience by improving mood and reducing physiological stress responses. However, the specific neurological mechanisms underlying this phenomenon are not yet fully understood. To study this, we have developed a rodent model of food reward, in which rats are given twice-daily access to 4 mL of a 30% sucrose solution. This model, which we call limited sucrose intake (LSI), has consistently been shown to reduce both behavioral and physiological stress responses in rats in a mechanism mediated by the basolateral amygdala (BLA). We have also found that LSI increases the expression of plasticity-related genes in inhibitory parvalbumin (PV) interneurons in the BLA. These cells play a major role in regulating the activity of stress-promoting BLA principal neurons, and their plasticity is largely determined by the perineuronal nets (PNNs) that surround them. Therefore, we sought to test whether LSI confers stress relief by altering PV PNNs. In a 2X2 design, adult male Long-Evans rats were either given LSI or water (control) for 5 days, and were then either exposed to 20-minute restraint stress or gently handled (control) once a day for 15 days. On day 20, brains were collected for immunofluorescent labeling of PV neurons, PNNs, and vGAT, a marker for presynaptic GABAergic neurons. LSI significantly increased the ratio of BLA PV neurons with PNNs (2-way ANOVA, main effect of drink = 0.009, main effect of stress = 0.06, drink X stress interaction = 0.952) while repeated restraint stress tended to have an opposite effect. The presence of PNNs was also associated with a significant decrease in the number of GABAergic puncta/μm on PV cells (unpaired t-test, p = 0.0142). Taken together, these data provide insight into a potential mechanism by which food rewards reduce stress responses. Specifically, LSI appears to increase PNNs surrounding BLA PV neurons while reducing GABAergic input onto these cells. BLA PV cells could consequently exert a greater inhibitory effect on the BLA's stress-excitatory output, thereby reducing stress responses.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR091.17/DD5

Topic: F.03. Stress and the Brain

Support: NIH R01 DK118292 (YMU)

Title: A larger amount of palatable food is needed to provide stress relief during Western diet-induced obesity

Authors: *I. L. RAINER[1,2], L. HERSHBERGER[3], M. PEDICINI[3], M. DAVIS[3], L. JAIN[3], Y. M. ULRICH-LAI[3];
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Abstract: Many individuals engage in stress-related eating to cope with stress, and this so-called 'comfort' feeding occurs to a greater extent in people who are overweight and obese. To study the mechanisms underlying this relationship, our group previously characterized a limited sucrose intake (LSI) paradigm in rats that reduces HPA axis stress responses in normal weight rats, but not in those with Western diet (WD)-induced obesity. The present work tests the hypothesis that a larger volume of sucrose drink is required to provide effective stress blunting during WD obesity. In all experiments, adult male Long-Evans rats were given WD (vs. normal chow) to induce obesity. After 8 weeks, rats with free access to their assigned diet and water were given additional, twice-daily access to sucrose drink. In experiment 1, 30% sucrose drink was offered in an unlimited volume for 30 min (time limited intake). After 2 weeks, rats received an acute restraint stress and tail blood was collected for the measurement of plasma corticosterone (Cort). Both lean and WD obese rats with time limited sucrose access drank a larger volume of 30% sucrose than that typically allowed in the LSI paradigm (4 ml). Moreover, these larger volumes effectively decreased the plasma Cort response to stress relative to water controls in both lean and WD obese rats. In experiment 2, rats were offered either 4 ml (standard LSI volume) or 6 ml (increased volume) of 30% sucrose drink (volume limited), or 4 ml of water as a control. In lean chow-fed rats, twice daily access to either 4 or 6 ml of sucrose drink reduced the plasma Cort response to restraint relative to water controls. In contrast, during WD obesity, HPA blunting occurred with twice-daily access to 6 ml, but not 4 ml, of sucrose drink. These data replicate prior findings that the sucrose volume typically used in the LSI paradigm (4 ml) does not produce effective stress blunting during WD obesity and extends this to show that an increased volume of sucrose drink recovers the effect. The results suggest the possibility of a vicious cycle whereby stress-related eaters with obesity may continually increase their consumption of palatable foods to maintain effective stress relief in the face of escalating obesity.

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Poster

PSTR091. Stress-Modulated pathways: Reward and Memory Circuits

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.18/DD6

Topic: C.10. Brain Injury and Trauma

Title: Efficacy of Fatty Acid-Enriched Diet Supplements to Attenuate Social Stress: A Genome-To-Phenome Analysis

Authors: N. CHAKRABORTY[1], A. GAUTAM[1], S. MUHIE[3], *S. KANNAN[2], S. ANN-MILLER[1], J. L. MEYERHOFF[1], M. JETT[1], R. HAMMAMIEH[1];
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Abstract: Social stress is emerging as a highly prevalent psychological health problem. Studies have suggested that diet choice can help in ameliorating social stress; yet the pertinent knowledge gap remains. Our previously published studies (PLos One, 2014 and JNB, 2017) suggested potential benefits of fish oil on neurogenesis and neuroprotection and potential drawbacks of unbalanced diet supplements were reported. Motivated by this, here we explore the efficacy for optimal dietary proportions of omega-3 (n3) vs. omega-6 (n6) polyunsaturated fatty acids (PUFA) to mitigate rodents' social stress (JNB, 2023). Three customized diets, namely n-3 PUFA-enriched diet (ERD, n3:n6= 7:1), balanced diet (BLD, n3:n6= 1:1) and standard lab diet (STD, n3:n6= 1:6) had similar textures, features and equi-caloric formulations. These three diets were separately supplied to three groups of C57BL/6j male mice from their weaning age until late adolescence. Afterwards, they were introduced to an Agg-E SS model. Thereof, the intruder C57BL/6j mouse co-housed with a resident aggressor SJL male mouse, as the naïve mouse was protected inside a small mesh-cage for 6 hours daily for 10 days. Three times per day, the aggressor and naïve mice came to a direct contact for one minute so that the naïve mouse can directly asses the threat. After 10d of Agg-E SS, their behavioral profiles were examined either a 1d (acute) or 4w (delayed) since the withdrawal of stress using a contextual cue paradigm (partition test). Compared to STD-, both ERD- and BLD-fed mice displayed certain resilience to acute and delayed effects of Agg-E SS. Indeed, the interactive effects of diet and stress played significant role in causing the variable manifestation of freezing, locomotion and withdrawal to periphery. PCA analysis of the behavioral profile revealed an undying trend among the diets, which was mirrored in the transcriptomic profile of hemibrain. Whole mouse genome assay was supplemented by functional analysis. The effects of STD included activated networks linked to mortality or morbidity, neurodevelopment disorder and premature aging; whereas the inhibited network linked to energy homeostasis. BLD showed positive impacts in controlling all of these networks. However, ERD demonstrated a differential effect; like STD, ERD inhibited energy homeostasis network. Further network analysis identified ERD as a potentially pro-inflammatory agent. The differential impacts of ERD vs. BLD were not well apparent in the behavioral profile of stressed mice, but the molecular analysis highlighted the discrepancies. This knowledge can further inform the potential long-term effects of PUFA enriched diets.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.01/DD7

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Science and Technology Innovation 2030 Major Program 2021ZD0200100
Strategic Priority Research Program of Chinese Academy of Sciences XDBS01030100
Shanghai Municipal Science and Technology Major Project 2018SHZDZX05
National Natural Science Foundation of China 82171899

Title: Functional roles of distinct basal forebrain neuronal population from global functional networks to behavioral performance

Authors: *C. TONG, Y. ZOU, Y. XIA, K. ZHANG, Z. LIANG;
Inst. of Neuroscience, CAS Key Lab. of Primate Neurobiology, Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: The basal forebrain (BF) plays a crucial role in various cognitive processes, including learning, memory, motivation, decision-making and attention. The function of cholinergic neurons in the BF has garnered most of the attention, however, there is a lack of comprehensive studies that investigate and compare cell-type specific regulations at both network and behavioral levels. In this study, we systemically characterized the whole-brain cerebral responses under BF cell-type specific manipulations, using our novel awake mouse optogenetic fMRI (opto-fMRI) setup. Thirty-six male mice were used in awake mouse fMRI and following behavioral studies, including 7 ChAT-Cre, 8 PV-Cre, 7 SOM-Cre, 7 VGLUT2-Cre and 7 wild-type mice. Combining with the anterograde tracing dataset from BF neurons, we found weak spatial correspondence between opto-fMRI activations and primary projections of BF neurons. Furthermore, based on the Allen connectivity atlas, we revealed triple low dimensional network organizations, rather primary projections, shaped the cell-type specific opto-fMRI activations, which derived from the secondary projections of BF neurons. Then, we also conducted the behavioral test in the arena with same optogenetic stimulation paradigm. We found apparent cell-type preference on the mouse behaviors, such as VGLUT2 and ChAT neurons prefer the externally oriented behaviors, i.e., locomotion and novel object exploration; but PV and SOM neurons prefer the internally oriented behaviors, i.e., quiet wakefulness and grooming. Moreover, we developed a novel method to predict the behavior related cerebral responses outside the magnet based on the opto-fMRI activation inside the magnet. Finally, we demonstrated the cell-type specific BF manipulation shapes triple low dimensional network organizations supporting behavioral variability. In summary, our findings have demonstrated that all subpopulations of BF neurons are capable of regulating cerebral functional dynamics and corresponding behaviors in the cell-type specific manner. This sheds light on the underlying mechanisms of such complex functions of BF and highlights the necessity to consider the effects of other types of BF neurons besides cholinergic neurons in neuroscience studies related to health or disease. Our method

presents a reliable and innovative approach for investigating the whole-brain responses to various free-moving behaviors and deep understanding the underpinnings of BF multiple (dys)functions in diseases.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

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Program #/Poster #: PSTR092.02/DD8

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01 DK132389-01

Title: Effects of carbohydrate metabolism on flavor nutrient conditioning

Authors: *A. KELLY, A. N. VALLE, R. M. SULLIVAN, M. OSTER, M. BAUGH, M. AHRENS, A. HANLON, A. DIFELICEANTONIO;
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Abstract: Post-ingestive consequences of food consumption have been identified as important drivers of food choice and preference. Many ultra-processed foods deliver calories rapidly and are highly rewarding. In literature surrounding substances of abuse, the speed at which a drug reaches the brain affects its abuse potential; this is known as the “rate hypothesis.” Here, we test whether the rate hypothesis of addiction may apply to food, specifically whether caloric availability, or the speed at which carbohydrate becomes available for use, contributes to food reward and preference. To do this, we use beverages with novel flavors mixed with either a slow metabolizing carbohydrate (maltodextrin and inulin; CS+Slow), a fast metabolizing carbohydrate (sucrose; CS+Fast), or no carbohydrate (sucralose; CS-). Participants are given each of these drinks 6 times to consume (conditioning period). 2 of these consumption periods occur during in-lab sessions. In one session, blood glucose is measured over one hour post-consumption. In another, we perform indirect calorimetry to assess post-consumption changes in substrate oxidation rates. At the post-testing session, changes in self-reported liking, wanting, and *ad libitum* intake of each beverage are recorded. Brain response to each flavor cue (without calories) is measured using fMRI at the post-test. We hypothesize the flavor paired with the CS+Fast will be the most liked, wanted, and consumed. We expect greater BOLD activation to the CS+Fast relative to the CS+Slow and CS- in the nucleus accumbens and hypothalamus. This is an ongoing study and, here, we present our preliminary analysis of the data.

Disclosures: **A. Kelly:** A. Employment/Salary (full or part-time):; Center for Health Behaviors Research, Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, VA, Translational Biology, Medicine, and Health Graduate Program, Virginia Tech, Roanoke, VA. **A.N. Valle:** A. Employment/Salary (full or part-time):; Center for Health Behaviors Research, Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, VA. **R.M. Sullivan:** A.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.03/DD9

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Ex vivo measurements verifies the ability of fNIRS to monitor brain water- and hemodynamics during clinical radiotherapy

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Abstract: Radiotherapy plays a crucial role in treating brain tumors. Currently, a significant obstacle revolves around the creation of cancer treatments that are specifically designed for each patient, and as a result, accurately assessing how an individual's brain responds to radiotherapy. Preliminarily we have shown that it is possible to measure the changes in blood flow in the brain during radiation treatment by using functional near-infrared spectroscopy (fNIRS). In this study, we wanted to determine whether this phenomenon is exclusive to living tissue or if it can also be observed in samples of blood, water, and air placed in a test tube during exposure to radiation. Furthermore, we more than tripled the number of human patients and measurements to validate our previous results.
We utilized a fNIRS device for the measurements. The patient was positioned in a supine position on the medical linear accelerator, and two NIRS channels with a source detection distance of 3cm were attached to the both sides of forehead above the mask. Furthermore, we exposed blood samples (n = 10), water samples (n = 3), and air (n = 3) confined in a test tube to radiation, and we measured the response using fNIRS with a similar setup.
During the study, we conducted a total of 126 measurements using fNIRS on 31 different brain

tumor patients (age 68.5 +- 11.5 years, 16 females) undergoing whole brain radiation therapy. Forward-intensity modulated radiation (FIMRT) technique was used with 6 MV x-ray beams at the dose rate of 600 MU/min. The measured raw fNIRS time courses were recorded at a sampling rate of 1 kHz and then converted into time courses that represented changes in water (H2O), oxygenated (HbO), deoxygenated (Hb), and total hemoglobin (HbT) concentrations using the modified Beer-Lambert law.
We did not observe any effects in the blood, water, or air samples, suggesting that the observed changes are specific to brain physiology. Furthermore, we verified our preliminary finding that the concentrations of hemoglobin-related components (HbO, HbR, HbT) increased during radiotherapy, indicating changes in blood flow and oxygenation. In addition, the concentration of water (H2O) clearly decreased.
Our findings confirmed the ability of fNIRS to monitor in real-time immediate changes in H2O, HbO, HbR, and HbT within the human brain during radiotherapy. We were unable to observe comparable responses in ex vivo blood, water, and air samples, indicating that the observed phenomenon is specific to living brain tissue. Our future objective is to analyze individual responses to radiotherapy with the intention of tailoring personalized treatments accordingly.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.04/DD10

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Regional changes in neurovascular coupling in MS patients

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Abstract: Neurovascular coupling in the brain involves acute localized blood flow increases in response to neural activity as a result of neural-astrocytic signaling. As such, it is a vital part of healthy neural function. Multiple sclerosis (MS) is known to disrupt the neural-glial-vascular system. Previous work has shown that MS patients exhibit changes in cerebral blood flow and metabolism during cognitive task performance. In this study, we examined whether MS patients would exhibit differences in neurovascular coupling compared to a healthy control (HC) group and whether these differences varied between regions. We sought to assess differences in

regional neurovascular coupling (NVC) variability between MS patients and HC group. MS and HC participants who met inclusion criteria were scanned using a 3T MRI scanner with a dual echo calibrated fMRI sequence which provided near-simultaneous measures for both cerebral blood flow (CBF) and BOLD signal during 3 in-scanner tasks to stimulate different regions of interest (ROI). These 3 regions were primary visual cortex, primary motor cortex, and dorsolateral prefrontal cortex (DLPFC). A hypercapnic gas challenge involving periodic inhalation of room air (4 min) and 5% CO_2 (6 min) permitted measures of cerebral metabolic rate of oxygen ($CMRO_2$). During imaging, participants performed block-design tasks of 3 different types corresponding to the 3 ROIs. Participants completed a visual task during which they viewed a radial checkerboard that flickered at 8 Hz, a motor task that involved bilateral finger-tapping to an auditory cue, and a digit symbol substitution task (DSST) that required matching a probe digit-symbol pair to a given key. Data were preprocessed, and average percent signal change from baseline was calculated in each voxel providing BOLD and CBF time-series. NVC ratio was calculated from the deoxyhemoglobin dilution model using CBF and estimated $CMRO_2$. Using repeated-measures ANOVA, significant differences in NVC ratio between regions were observed in MS patients (F[22]= 10.49, p<.001) but not in healthy controls (F[8]-1.87, p= .215). Post-hoc t-tests comparisons in MS patients revealed the motor cortex NVC ratio to be significantly higher than visual cortex and DLPFC, and no significant differences were detected between the DLPFC and visual cortex. These results suggest that MS induces changes in regional heterogeneity of task-evoked neurovascular coupling that may affect cognitive performance.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

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Program #/Poster #: PSTR092.05/DD11

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: A Probabilistic Tractography Map of the Superior Longitudinal Fasciculus Subdivisions

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Abstract: The superior longitudinal fasciculus (SLF) is a major association fiber tract connecting the prefrontal cortex (PFC) and the posterior parietal cortex (PPC) in the human brain. Past monkey histological and human neuroimaging studies have revealed three separate subdivisions of the SLF, organized from dorsomedial to ventrolateral. However, since the majority of human neuroimaging studies often consider the SLF as one homogenous unit, the

functional characteristics of each SLF subdivision remain unclear. Here, we attempt to create a nuanced probabilistic atlas of the SLF subdivisions in each hemisphere and differentiate the relationship between cognitive functioning and each SLF subdivision. Using diffusion data from the Human Connectome Project Aging (HCP-A) cohort (N = 57, Age = 59.9 ± 15.5, 34F/23M), we conducted probabilistic tractography between three sets of PFC ROI's and three sets of PPC ROI to model the SLF subdivisions for both left and right hemispheres. Local tractography was conducted for each subject, normalized to the MNI152 template, then binarized and averaged across subjects to make the final mask for each subdivision. We used a 2-way ANOVA to assess the main effects and interactions between SLF subdivision and hemisphere on FA levels and number of tracts. Finally, we used multiple regression analyses to assess the relationship between SLF subdivision connectivity and cognitive functions. The probabilistic tractography delineated three separate SLF subdivisions for each hemisphere, resulting in six probabilistic maps. The ANOVA revealed main effects of hemisphere and section, but no interaction. SLF I showed the highest average fractional anisotropy (FA) in comparison to the other two subdivisions. SLF I had the lowest number of tracts, while SLF II had the highest number of modeled tracts in each hemisphere. Regression analyses revealed FA in left SLF I ($\beta = -61.1$, $p < .036$), as well as both the left ($\beta = -64.3$, $p = .026$) and right ($\beta = -56.6$, $p = .018$) SLF II were associated with executive functioning scores. The FA of left SLF II ($\beta = 98.6$, $p = .034$) and right SLF III ($\beta = 117.8$, $p = .004$) were associated with episodic memory. Lastly, the number of tracts in the left ($\beta = -.05$ $p = .014$) and right ($\beta = -.017$ $p = .002$) SLF I were associated with processing speed and executive functioning scores, respectively. We present a probabilistic atlas for the three SLF subdivisions for each hemisphere using diffusion tractography. An accurate and accessible probabilistic atlas would be useful for studying the more nuanced functional characteristics of the SLF. Our preliminary findings suggest there are separable structural and functional differences in the SLF subdivisions.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

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Program #/Poster #: PSTR092.06/DD12

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: USC Neurorestoration Center
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Title: Evaluation of image registration methods applied to cerebral functional ultrasound imaging

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Abstract: Functional ultrasound imaging (fUSI) is an emerging technology that represents a new platform for neuroimaging with high sensitivity and spatiotemporal resolution. While fUSI enables a wide range of pre-clinical and clinical applications, the lack of normalization processes that enable effective alignment of fUSI images into a generic anatomical template limits functional analysis. Therefore, the preponderance of fUSI studies is restricted to either averaging activity within selected regions of interests (ROIs) or ROI-ROI functional connectivity analysis. Increasing utilization of fUSI requires developing techniques for co-registering power Doppler vascular maps from different sessions and subjects, to enable more advanced voxel-wise statistical analysis and generation of statistical parametric maps (SPMs) across sessions and subjects. In the current study, we evaluated the effectiveness of 7 rigid and non-rigid image registration techniques that have been widely used in biomedical neuroimaging. We employed 2D sagittal whole-brain fUSI data acquired from 82 male 8-12-week-old C57BL/6 mice, which are head-fixed and under anesthesia. The fUSI data were acquired using 128-channel linear ultrasound transducer array, with 15 MHz center frequency and 0.1 mm pitch. This technique enables a large field of view (12.8 mm width, 10 mm depth and 400 μm plane thickness) while maintaining high spatial resolution (100 μm x 100 μm in-plane). The transducer was placed on the intact skull and skin along a sagittal plane on the right side. The image plane was selected to record brain activity from memory-related regions including the medial prefrontal cortex (mPFC) and hippocampus. We extracted 2 min worth of fUSI image-frames from each mouse and aligned each frame to 14 reference images, utilizing the 7 image registration techniques. The reference images were selected from mice recordings that revealed high image quality and contrast details. All registration techniques were preceded by periodic and drift motion correction, as well as a low-pass filter to remove high frequency fluctuations. These techniques were visually compared and evaluated by comparing the cross-correlation between the pre- and post-registration frames and the reference frames. The results showed that the post-registration frames were significantly improved over the pre-registration frames for all methods. However, the non-rigid registration algorithm Imregdeform outperforms the other techniques. Overall, our study provides the first comparison of image registration methods for fUSI data, promoting more effective use of fUSI in both research and clinical settings.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

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Title: Resting state fMRI and visual stimulation evoked fMRI

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Abstract: Awake rodent fMRI has been increasingly applied as a promising non-invasive imaging tool to investigate the organization of functional networks, thus providing the mechanistic understanding of the neural basis of brain-wide neurovascular coupling in both healthy and diseased animal models. This procedure could avoid impact on neural activity and hemodynamic responses by anesthetic agents. Therefore, the specific goal of this study is to implement an awake mouse fMRI protocol/data analysis both during resting state and under visual stimulation, with a relatively short training paradigm and without modification of conventional scanner setup. All procedures in this study were conducted in accordance with guidelines set by the Institutional Animal Care and Use Committee of Michigan State University. 3 Mice were habituated for 7 days: 4 days in the mock scanner with FLASH/EPI/RARE sound and 3 remaining days in the 7T Bruker scanner. We evaluated this protocol by measuring the fMRI signal over the whole brain first using task fMRI with visual stimulation of 5 Hz on both eyes and then using resting-state fMRI (rs-fMRI). The fMRI data from the last day with 30-min fMRI scanning (spatial resolution: 0.3 mm × 0.3 mm × 0.5 mm, 20 slices, TR: 1s) in wakefulness were used for analysis. Each rs-fMRI scan acquired 400-time points (6 min 40s). The preprocessing procedures for rs-fMRI include motion correction, despike, t-shift, spatial blurring, 0.01-0.1 Hz bandpass filtering in AFNI, and ICA denoising in FSL. In the task fMRI, we observed a robust evoked BOLD-fMRI in the primary visual cortex (V1), higher-order visual area (V2), dorsal lateral geniculate nucleus (LGd), and superior colliculus (SCs). In the rs-fMRI, we observed a strong default-mode network, including the prelimbic cortex, cingulate cortex, posterior parietal cortex, and retrosplenial cortex. In summary, this awake mouse protocol allows whole-brain mice imaging in the awake state without modifications to the scanner's hardware, using a relatively short training paradigm.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: JP19dm0207065
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Title: Development of a novel olfactory stimulation fMRI system for common marmosets.

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Abstract: Background: Olfactory dysfunction is associated with the earliest stages of neurodegenerative diseases such as Alzheimer's and Parkinson's disease and is reported as a strong predictor of cognitive decline. Marmosets, small primates often used in brain function research, can serve as genetically modified models for neurodegenerative diseases. Despite recent findings that the olfactory nerve maps of marmosets more closely resemble that of humans than rodents, olfactory pathway activity during odor stimulation remains unreported, mainly due to hardware constraints with small-diameter MRIs. We modified a non-invasive functional MRI (fMRI) holder (reported in SfN 2021) and developed an olfaction testing system using odor-stimulated fMRI imaging with a small aperture MRI machine.**Methods:** We performed functional MRI tests with olfactory stimulation on three marmosets. Before the fMRI experiments, the marmosets were acclimated to the head holder. All holder components were 3D-printed and designed to have an outer diameter of ≤ 72 mm. The holder featured a double helmet: an inner one housing a receiver coil and an outer one to minimize head motion. Two tubes were passed through the fixed parts of the head and extended near the marmoset's nose. One tube was used for inflow, the other for outflow. A compressor was used to feed the vaporized alinamin solution through the inlet, and odor presentation controlled by a balloon placed 50 mm in front of the nose. Each 60-second fMRI test trial, half without stimulation and half with stimulation, enabled the analysis of signal value changes in 16 cortical regions.**Results and discussion:** The dual helmet system restricted head movement to < 0.5 mm. The outflow tube and the balloon valve installed in the inflow tube controlled high odor concentrations and allowed high temporal resolution analysis. fMRI analysis showed a rapid signal value increase within five seconds of olfactory stimulation in seven olfactory-related regions, including the olfactory bulb, piriform cortex, thalamus, and orbitofrontal cortex. The outflow tube and the balloon valve installed in the inflow tube made it possible to control the high odor concentration and analyze it with high temporal resolution. On the other hand, brain regions of the gustation and the sense of touch also indicated increased signal values. The connection between smell and taste and the effect of wind could be the cause. This olfactory stimulus fMRI would be useful to clarify the relationship between olfactory dysfunction and dementia in nonhuman primates.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSERC
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Title: Investigating task-free functional connectivity patterns in newborn infants

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Abstract: Functional imaging studies conducted on preterm and term-born infants indicate that the full repertoire of resting-state functional networks, especially motor and somatosensory networks, emerge in the third trimester and mature into their adult-like forms at term. More specifically, as gestational age increases, these networks transition from being unilateral (within one hemisphere) to bilateral (across both hemispheres). The integrity and structure of these networks have been linked to neurological health outcomes in neonates. As such, monitoring the development of these networks is especially important. Functional near-infrared spectroscopy (fNIRS) has emerged as a neuroimaging technique that utilizes near-infrared light to measure changes in oxygenated (HbO) and deoxygenated hemoglobin concentrations (HbR), providing an indirect measure of neural activity. Unlike other imaging methods, fNIRS is silent and allows for naturalistic monitoring of neural activity at bedside, making it particularly useful for studying awake infants. Therefore, our objective was to build upon previous findings regarding the development of functional networks in awake preterm and term-born neonates using fNIRS. As part of a larger study involving multiple clinical cohorts, we conducted fNIRS scans on 29 term-born neonates (13 females, 36+0 - 42+1 weeks gestational age) in the Post-Partum Care Unit within the first few days after birth, while also collecting extensive demographic information. We utilized 8 LED sources and 8 detectors to record from sensorimotor networks in both hemispheres. Data were resampled to 4 Hz and used to calculate spontaneous functional connectivity (sFC). A group level sFC > 0 statistical test showed positive intra-hemispheric and negative inter-hemispheric connectivity ($q < 0.05$). Using a Linear Mixed Effects Model, we then investigated the relationship between sFC and gestational and post-gestational age while controlling for sex and subject effects. Isolated channel pairs within and across both hemispheres whose connectivity showed a significant association with gestational and post gestational age, however only post-gestational age was associated with stronger connectivity in the left hemisphere ($p < 0.004$). Our findings highlight the importance of considering the developmental changes in functional networks in awake infants and demonstrates the potential of fNIRS as a valuable tool for studying neural activity in a naturalistic settings in neonates.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

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Title: Diurnal variation of brain activity in the human suprachiasmatic nucleus

Authors: *S. OKA[1], A. OGAWA[1], T. OSADA[1], M. TANAKA[1], K. NAKAJIMA[1,6], K. KAMAGATA[2], S. AOKI[2], Y. OSHIMA[6], S. TANAKA[6], E. KIRINO[7], T. J. NAKAMURA[8], S. KONISHI[1,3,4,5];
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Abstract: The suprachiasmatic nucleus (SCN) is the central clock for circadian rhythms. Animal studies have revealed daily rhythms in the neuronal activity in the SCN. However, the circadian activity of the human SCN has remained elusive. In this study, to reveal the diurnal variation of the SCN activity in humans, the SCN was localized, and its activity was investigated using perfusion imaging. We scanned each participant four times a day, every six hours, and higher activity was observed at noon while lower activity was recorded in the early morning. The SCN activity was then measured every thirty minutes for six hours from midnight to dawn and showed a decreasing trend and was comparable with the rodent SCN activity after switching off the lights. These results suggest that the diurnal variation of the human SCN follows the zeitgeber cycles of mammals and is modulated by physical lights rather than the local time.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

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Program #/Poster #: PSTR092.11/DD17

Topic: H.06. Social Cognition

Support: FRN Grant 148365

Title: Identification of functional homologies between marmosets and humans using movie-driven ultra-high field fMRI

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Abstract: The primate brain is composed of a dense mosaic of brain areas often distinguished according to their function, cytoarchitectonic structure, or connectivity. Outlining its functional organization is thus crucial in understanding how and where information is processed at the cortical level. Identifying the functional homologies existing between different primate species is a fundamental step to understand the evolution of our cognitive functions and to develop effective and reliable comparative studies.To characterize the functional cortical architecture of the common marmoset (Callithrix jacchus), we utilized ultra-high field (9.4T) functional MRI data obtained from 9 awake marmosets as they were presented with a 33-minute movie featuring a broad range of visual and acoustic stimuli. This same video was shown to 19 healthy human participants while we recorded their BOLD responses using a 7T scanner.By adopting a data-driven hierarchical clustering approach, we identified several functional networks in both species, each related to the processing of different types of sensory information and various cognitive processes. Clustering was accomplished by averaging the 1325 time-points composing the average time-courses from a complete scan session for each gray matter voxel. Using these average time-courses, we computed a 2D correlation matrix between the time-course of all the cortical voxels. We then measured the standard Euclidean distance between each pair of correlation values and constructed a hierarchical cluster tree using Ward's method for linkage. Among the clusters thus defined, some overlap with previously described sensory areas, such as the primary auditory or the visual cortices, while others encompass areas involved in specific functional processes like the face/body-parts network or the somato-motor network.Significantly, the use of the same naturalistic video and the same repetition time (TR = 1.5 seconds) for both humans and marmosets enabled us to investigate the functional cortical homologies between the two species. We achieved this by correlating the time-course of each cluster identified in the marmoset brain with that of each cluster in the human cortex, thus identifying cortical areas presenting a similar pattern of activity.The functional parcellation presented here, therefore, 1) establishes a reliable foundation for localizing cortical areas characterized by different functional features in both humans and marmosets, and 2) underlines functional cortical homologies between the two species. This provides a crucial interpretative framework for future comparative studies involving this small New-World monkey.

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Poster

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.12/DD18

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Functional Fingerprinting of Neuroactive Drugs

Authors: *E. MACNICOL[1], D. DI CENSO[1], E. WALTERS[1], A. KALISZEWSKA[1], E. KIM[1], K. ILIC[1], M. E. SERRANO NAVACERRADA[1], M. M. PETRINOVIC[1], S. C. R. WILLIAMS[1], M. MESQUITA[1,2], **D. CASH**[1];
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Abstract: Research objective and rationale Drug discovery in neuroscience is ethically and economically prohibitive but magnetic resonance imaging (MRI) could bridge the “bench to bedside” gap. However, small animal MRI is often not sufficiently standardised to facilitate comparison between studies. Thus, the exploratory research objective is to identify neuroimaging *fingerprints for* well-known neuroactive drugs, against which novel therapeutics can be compared. **Methods** Male Sprague Dawley rats (312±49g) were scanned (9.4 T Bruker) under a combination of isoflurane and medetomidine. A drug [vehicle control, n=12; MK-801 (0.3mg/kg), n=15; clozapine (5mg/kg), n=15; ketamine (25mg/kg), n=15] was delivered subcutaneously immediately before acquiring resting state functional MRI (rs-fMRI) data and quantitative cerebral blood flow (CBF) maps. Functional connectivity (FC) was estimated in 150 anatomical regions of interest (ROIs) for voxelwise and pairwise comparisons including network-based statistics (NBS) and graph theory. Mean CBF was calculated voxelwise and for each of 22 ROIs.Each drug was compared to vehicle independently. Voxelwise differences were calculated with statistical parametric mapping using a two-tailed independent t-test. Differences in pairwise FC and graph theoretical measures were assessed non-parametrically by permuting vehicle and drug. Differences in regional CBF were calculated with a mixed-effects model looking at the effect of group (between-subject), region (within-subject), and their interaction as factors. Post-hoc multiple comparisons were controlled using Dunnett’s test. **Results** We show that administering drugs, known to affect targets across neurotransmitter systems and with different PK/PD, causes various changes to CBF and FC in rats. The effects of region ($p<0.001$), drug ($p=0.002$), and their interaction ($p<0.0001$) were significant. Ketamine and MK-801 increased CBF in almost all regions while clozapine showed a more select pattern of regional increases, mostly within the basal ganglia and fronto-parietal cortices. Ketamine also had the biggest changes in FC compared to vehicle. NBS of pairwise connectivity showed a strong potentiation of inter- and intra-hemispheric connections compared to vehicle ($p=0.0004$). **Conclusions** Using this drug fingerprinting approach, we show the largest effects on CBF and FC are by clozapine, and highlight local CBF and FC changes induced by MK801 and ketamine. All data will be curated for an openly available database of standard pharmacological MRI responses to well-known drugs. Such responses can be used as a reference system for profiling novel neuroactive compounds.

Disclosures: **E. MacNicol:** None. **D. Di Censo:** None. **E. Walters:** None. **A. Kaliszewska:** None. **E. Kim:** None. **K. Ilic:** None. **M.E. Serrano Navacerrada:** None. **M.M. Petrinovic:** None. **S.C.R. Williams:** None. **M. Mesquita:** A. Employment/Salary (full or part-time):; L&M Data Science Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); L&M Data Science Ltd. **D. Cash:** None.

Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.13/DD19

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Oxygen manipulation and brain activity: a multi-modal investigation

Authors: *D. GRAHAM[1,2,3], G. SMERDON[3], A. D. SMITH[1,2], H. WINDMILL[1,2], S. D. HALL[2,1];
[1]Sch. of Psychology, Univ. of Plymouth, Plymouth, United Kingdom; [2]Brain Res. Imaging Ctr., Plymouth, United Kingdom; [3]DDRC Healthcare, Plymouth, United Kingdom

Abstract: The human brain, is the most oxygen-sensitive organ, consuming approximately 20% of the total oxygen supply despite representing only 2-3% of the body's mass. Hyperbaric Oxygen Therapy (HBOT), a medical intervention in which pure oxygen is inhaled in a pressurised hyperbaric chamber, has shown promise for a range of neurological treatments. However, a comprehensive understanding of the neurological and cognitive implications of altered oxygen levels, especially in the context of HBOT, remains unclear. This study utilises a multi-modal approach to understand the brain's response to oxygen modulation. A set of experiments were conducted, manipulating normobaric oxygen levels (10.5%, 21%, and 100%). These experiments integrated a range of techniques, including standardised cognitive testing, EEG, TMS, and MRI; encompassing arterial spin labelling and spectroscopy. Additionally, the effect of HBOT on neural oscillations was examined using mobile EEG technology in conjunction with a hyperbaric chamber. Our findings indicate unique patterns of changes in corticospinal excitability, cognitive performance, perfusion, and metabolic shifts under different oxygen conditions. Importantly, we also observed changes in specific neural oscillations and connectivity patterns associated with HBOT, suggesting distinct, state-dependent neural dynamics under varying oxygen conditions. The results provide novel insights into the effects of altered oxygen levels on brain function and cognition. These findings enhance our understanding of the application of HBOT, potentially paving the way for optimised therapeutic protocols for neurological conditions. The multi-modal approach deployed here can serve as a comprehensive framework for future explorations into the neurobiology of oxygen modulation. And thus, will help develop an evidence base for the applicability of HBOT to treat a range of neurological disorders.

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Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.14/DD20

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH-NIMH R01-MH124115
NIH-NINM R01-MH122512
Principal Research Fellowship funded by the Wellcome Trust 091188/Z/10/Z
Virginia Tech Foundation Seale Innovation Award

Title: Novel signal detection of commonly used substances in the human brain through a Machine Learning Enhanced Voltammetry Approach

Authors: *N. RAHEJA[1,2], J. WONG[2], S. BATTEN[2], T. TWOMEY[2], T. LOHRENZ[2], R. MONTAGUE, Jr[2];
[1]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [2]Fralin Biomed. Res. Inst. at VTC, Virginia Tech., Roanoke, VA

Abstract: In everyday life, people consume a variety of psychoactive substances, whether for recreational or pharmacological purposes. Common recreational substances include caffeine and nicotine, while common pharmacological treatments include SSRIs and antipsychotic medications. Despite the mass consumption of these common substances, the in-vivo neurochemical effect of these compounds remains largely unknown. This is largely due in part to a technological inability to measure in the human brain real-time changes of these compounds, as well as their modulatory effects on major neurotransmitter systems. Using a novel machine learning enhanced voltammetry (MLEV) approach, we built high-quality concentration estimation models of a vast range of ubiquitous drugs and associated neuromodulators. Models trained on these in-vitro data are currently being deployed on surgically implanted standard of care clinical depth electrodes in patients undergoing intracranial epilepsy monitoring (EMU) to produce in-vivo concentration estimates of these psychoactive substances and their downstream effectors in brain regions such as the amygdala, hippocampus, and cingulate cortex. These high-quality concentration estimation models provide a proof-of-concept for measuring the real-time dynamic mechanism of actions of these drugs and their associated neuromodulators in awake, conscious humans.

Disclosures: **N. Raheja:** None. **J. Wong:** None. **S. Batten:** None. **T. Twomey:** None. **T. Lohrenz:** None. **R. Montague:** None.

Poster

PSTR092. Functional Imaging: Human and Nonhuman Mammals

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.15/DD21

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: RGPIN-2020-06930

Title: Increasing the frequency of somatosensory stimulation decreases the neural responses and causes divergence of the neural and hemodynamic responses

Authors: *A. BORTEL[1,2], A. SHMUEL[2,1];
[1]Montreal Neurolog. Inst., Montréal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

Abstract: In the cerebral cortex, pyramidal cell activity is coordinated through a balance of inhibitory and excitatory inputs. GABAergic interneurons generate inhibitory postsynaptic potentials that attenuate the activity of other neurons in the cortex and modulate cortical excitability. A commonly accepted hypothesis regarding the mechanisms underlying the functional MRI (fMRI) response is that the amplitude of the hemodynamic response is also connected to the balance between excitation and inhibition. Another commonly accepted hypothesis considers the Local Field Potentials (LFP) as the main indicator of neural activity that correlates with the fMRI response. Here we evaluate these two hypotheses by characterizing the effect of excessive activation of cortical neurons on neural and hemodynamic responses. To this end, we performed simultaneous neurophysiological recordings and optical imaging in area S1FL of C57BL/6 mice. Electrical stimuli were delivered to the forepaw, with a pulse frequency of 2, 4, 6, 8, and 10 Hz and stimulus intensity of 1 or 2 mA. Stimulus duration was set for 5s, or the duration required for delivering 20 pulses for each frequency. We analyzed the impact of the stimulation frequency, duration, and strength on cortical excitability and the blood volume (CBV), LFP, and multi-unit activity (MUA) responses following peripheral somatosensory forepaw stimulation. We observed a divergence of hemodynamic and neural responses to increasing stimulation frequencies. CBV responses were induced by all stimulation frequencies, with the largest amplitude obtained in response to stimulation at 4 Hz. In contrast, LFP and MUA responses decreased with increasing frequency stimulation. Stimulation at 2 Hz and 4 Hz evoked high-amplitude, regular LFP responses to all stimulation pulses. Stimulation at 6 Hz induced smaller and irregular LFP responses. Stimulation at 8 - 10 Hz resulted in LFP responses only to the first 1-4 pulses. The hemodynamic and LFP responses to 20 pulses or 5s-long stimulation were similar for the same frequency. Stimulation with 2 mA evoked LFP and hemodynamic responses of higher amplitudes relative to the responses elicited by stimulation with 1 mA. We hypothesize that high-frequency stimulation of cortical pyramidal neurons increases cortical inhibition. The hypothesized scenario is that the excitatory input to pyramidal cells decreases but inhibitory GABAergic tone increases. In contrast to the decrease in the neural responses with increasing stimulation frequency, the hemodynamic responses remain approximately constant, possibly because of the interneurons' contributions to neurovascular coupling.

Disclosures: **A. Bortel:** None. **A. Shmuel:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.01/DD22

Topic: F.06. Autonomic Regulation

Support: 1UG3DA050303-01
R01-DA041781

Title: Investigation of Peripheral Mechanisms Underlying Opioid-Induced Respiratory Depression

Authors: ***B. RUYLE**[1], M. TAHIRKHELI[2], S. MASUD[2], J. MODH[2], J. MORON-CONCEPCION[2];
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Abstract: Millions of Americans suffer from Opioid Use Disorders (OUD) and face a high risk of accidental overdose, which can cause opioid-induced respiratory depression (OIRD). Synthetic opioid opioid-related overdose deaths continue to rise, thus it is critical to understand the mechanisms by which fentanyl induces respiratory depression. We previously showed that the peripherally-restricted opioid receptor antagonist naloxone methiodide (NLXM) prevents and reverses OIRD to a similar degree as naloxone. We aim to understand the peripheral contributions underlying OIRD. The vagus nerve expresses mu opioid receptors and terminates in the nucleus of the solitary tract, a critical mediator of basal and reflex-evoked cardiorespiratory function. We used a chemogenetic approach to express Gq-DREADDS in the nodose ganglia and vagal afferent fibers of rats. Fentanyl produced rapid cardiorespiratory depression, characterized by decreased oxygen saturation, heart rate and respiratory rate. Intravenous CNO restored cardiorespiratory parameters faster than saline, suggesting that fentanyl disrupts a vagal-brainstem circuit which contributes to prolonged OIRD. To obtain further insight into the peripheral contributions to OIRD, separate groups of rats underwent three day conditioned place preference (CPP) consisting of a pretest, test day, and posttest. On the test day, a divider was placed in the middle of the CPP box. Fentanyl was administered in home cages. Four minutes later, rats were moved to one side of the CPP box and administered either naloxone or NLXM. The following day, the divider was removed and rats were allowed to explore the entire CPP box. Rats displayed an aversion to the naloxone-paired side, and this was not observed in NLXM-treated rats. These findings provide insight into peripheral mechanisms that contribute to OIRD and how antagonism of these receptors could be a promising therapeutic strategy for managing OIRD by sparing the CNS-driven acute opioid withdrawal generally observed with the use of naloxone.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.02/DD23

Topic: F.06. Autonomic Regulation

Support: NIH Grant R01HL146169

Title: Xylazine in Fentanyl Mixtures: A Growing Concern in the Opioid Crisis and the Use of Oxytocin for Reversing Respiratory Depression

Authors: *J. B. ESCOBAR[1], O. DERGACHEVA[3], J. WAINWRIGHT[4], D. MENDELOWITZ[2];
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Abstract: Xylazine in Fentanyl Mixtures: A Growing Concern in the Opioid Crisis and the Use of Oxytocin for Reversing Respiratory Depression
Joan Escobar, Olga Dergacheva, John Wainwright and David Mendelowitz
The opioid epidemic in the United States has resulted in devastating consequences, with over 500,000 Americans losing their lives since 1999, affecting countless families and communities. Synthetic opioids, particularly fentanyl, play a significant role in the escalation of opioid overdoses. However, recent concerns have emerged regarding the prevalence of the veterinary tranquilizer xylazine in fentanyl mixtures, which is not counteracted by naloxone. With 100,000 annual deaths in the United States from opioid overdoses in the United States, and the presence of xylazine-laced fentanyl in 48 out of 50 states, where approximately 23% of fentanyl powder contains xylazine, further research to counteract the effects of combined xylazine with fentanyl are needed. In this study, two groups of male Sprague Dawley rats (n=8) received a combination of intraperitoneal (IP) fentanyl (0.5 mg/kg) and xylazine (1 mg/kg). 10 minutes post-injection, group one was given IP Oxytocin (100 nmol/kg) while group two received IP saline. Respiratory function was quantified using a whole-body plethysmography system in unrestrained and freely moving animals.In untreated animals, fentanyl and xylazine decreased respiratory frequency by 80%, and tidal volume decreased 25%. These drugs also induced an increase in apnea and hypopnea occurrence. In animals given oxytocin, breathing frequency was 20% higher, and the occurrence of apneas was 75% lower compared to untreated animals. These results indicate oxytocin is a promising treatment to mitigate opioid-induced respiratory depression in emergency and/or clinical settings. Further exploration of oxytocin’s effectiveness and

implementation strategies could pave the way for improved interventions and better outcomes in combating the detrimental effects of the opioid crisis and the growing prevalence of xylazine.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.03/DD24

Topic: F.06. Autonomic Regulation

Support: NIH Grant R21EB024793
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NIH Grant T32-GM008602
Roneet Carmell Memorial Endowment Fund

Title: Brain-heart connections at the edges of consciousness

Authors: *J. D. YI[1], R. LOTFY[1], S. KHATAMI[1], A. BAZRAFKAN[1], M. RAFI[1], Y. AKBARI[2]; [1]Univ. of California, Irvine, Irvine, CA; [2]Neurol., UC Irvine, Irvine, CA

Abstract: Cardiac arrest (CA) affects &gt500,000 Americans per year and has abysmal survival rates (10-20%). Withdrawal of care due to neurological sequelae is a leading cause of mortality among resuscitated patients. The brain must receive perfusion continuously within a narrow range of cerebral perfusion pressures or else irreversible damage occurs. The autonomic nervous system controls the heart and vasculature to optimize cerebral perfusion to meet the metabolic demands of the brain, forming the so-called “brain-heart connection.” During CA and after successful cardiopulmonary resuscitation (CPR), the brain-heart connection is put to the ultimate test of perfusing and saving the dying brain. Using a rat model of asphyxial CA & CPR and multimodal physiological monitoring, we have begun to identify common but poorly understood events in the process of dying and resuscitation where surges of cortical electrical and metabolic activity are tightly associated with cardiovascular events. In this model, adult male Wistar rats (N = 9 unless otherwise stated) were mechanically ventilated via endotracheal intubation and monitored with electrocorticography (ECoG), electrocardiogram (ECG), blood pressure (BP), intracranial pressure (ICP), laser speckle imaging of cerebral blood flow (rCBF) and spatial-frequency domain imaging of cerebral metabolic rate of oxygen (CMRO2). Asphyxial CA was induced by shutting off the ventilator for 7 minutes. Around 21 ± 7 s after the start of asphyxia, ICP spiked to 20 ± 5 mmHg (mean ± st. dev., baseline 13 ± 3 mmHg, p &lt 0.001 paired t-test). This ICP spike preceded precipitous hypotension, which in turn was coupled to a surge in bilateral frontal ECoG wavelet coherence in the beta band (13-30 Hz, 33 ± 3 s post-asphyxia, N = 5). Anoxic spreading depolarization (SD, at 126 ± 37 s, N = 7) overlapped with the onset of sustained premature heart beats (latency between SD & arrhythmias = 7 ± 55 s, N = 5). Finally,

around 25-35 minutes after CPR, ECoG burst-suppression was observed where a subset of rats had occasional bursts phase-locked to surges in BP (N = 4), ICP (N = 4), and rCBF (N = 3). While seemingly unrelated, we hypothesize these events are unified as they represent transient perturbations in autonomic signaling coupled to cortical activity. To our knowledge, none of these coinciding neural and hemodynamic events have been reported (except case reports of ICP surges in burst-suppression in humans). However, their future exploration as ultra-early prognostic or therapeutic or targets for CA care is promising as our preliminary data suggests modifying cerebral perfusion early in CA and early after CPR can have profound effects on neurological outcome.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.04/DD25

Topic: F.06. Autonomic Regulation

Support: NSF Grant CMMI 1916814

Title: Aortic stiffness increases in a mouse model of spinal cord injury

Authors: S. SWAMINATHAN[1], P. MATHIEU[2], R. SAPP[2], R. REYES[1], C. REANDEAU[1], ***J. RICARD**[1], V. BRACCHI-RICARD[1], A. M. CLYNE[2];
[1]Drexel Univ., Philadelphia, PA; [2]Univ. of Maryland, College Park, MD

Abstract: Locomotor function impairment is not the only hurdle spinal cord injured (SCI) patients face. Spinal cord injury affects multiple organ systems, including the cardiovascular system. Compared to able-bodied populations with similar age, blood pressure, weight and physical activity, SCI patients have accelerated arterial stiffening, correlating with an elevated risk of cardiovascular diseases. Arterial stiffness occurs when vascular smooth muscle cells (vSMC) in the arterial wall change their phenotype and start remodeling the extracellular matrix by depositing more collagen and releasing matrix metalloproteinase 12 (MMP12) enzyme that degrades elastin fibers. It is believed that the inflammatory status of the perivascular adipose tissue (PVAT) surrounding the aorta can modulate vSMC phenotype; however, the mechanism by which SCI may increase PVAT inflammation is largely unknown. We hypothesized that SCI-induced chronic inflammation and/or alteration of the sympathetic nervous system (SNS) may induce PVAT inflammation thereby promoting arterial stiffness through modulation of vSMC activity. Using atomic force microscopy, we show increased arterial stiffness in C57Bl/6J WT mice 4 weeks following a moderate thoracic spinal cord contusion. WT SCI mice showed increased PVAT inflammation as measured by the increased presence of CD68+ cells. Blocking TNFR1 signaling within the spinal cord decreased arterial stiffening 4 weeks post-SCI,

suggesting that central inflammation plays a role in aortic stiffening possibly by regulating peripheral inflammation through SNS modulation. Arterial stiffness was also reduced when SCI was induced either in mice lacking TNFR1 or MMP12. In summary, SCI-induced inflammation likely leads to accelerated arterial stiffening and subsequent cardiovascular disease. This mechanistic insight can lead to intervention strategies to reduce the risk of cardiovascular diseases in the SCI population.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.05/DD26

Topic: F.06. Autonomic Regulation

Support: NIH Grant HL098602
NIH Grant HL128454 (DDK)

Title: Corticotropin-releasing hormone and oxytocin enhanced nTS activity in rats subjected to chronic intermittent hypoxia.

Authors: *P. BARCELLOS-FILHO, H. A. DANTZLER, E. M. HASSER, D. D. KLINE; Dept. of Biomed. Sci. and Dalton Cardiovasc. Res. Ctr., Univ. of Missouri, Columbia, MO

Abstract: Chronic intermittent hypoxia (CIH) increases sympathetic activity, blood pressure, and respiration. The nucleus tractus solitarii (nTS) integrates peripheral signals and receives modulating input from the paraventricular nucleus of the hypothalamus (PVN). nTS-projecting PVN neurons that are activated by hypoxia contain oxytocin (OT) or corticotropin-releasing hormone (CRH), but their specific influence on nTS activity during CIH is unclear. We hypothesized that OT or CRH individually increases nTS activity, and their combined influence would further enhance activity. We also expected these responses to be enhanced by CIH. Male Sprague-Dawley rats (~3 wks) were exposed to 10d normoxia (21% O2) or CIH (~30s of 6% O2, 10x/hr, 8 h/day). Recorded events were examined during exogenous OT and CRH or their receptor block (OTR-x, CRHR2-x). In nTS slices, extracellular discharge from multi electrode array (MEA) recording increased by OT and its co-application with CRH across the nTS after normoxia. Following CIH, OT and CRH alone, and their co-application increased firing rate, and the response to OT+CRH after CIH was greater than in normoxia slices. Fura-2 calcium imaging in primary dissociated nTS neurons demonstrated enhanced responses to OT+ CRH following CIH vs normoxia. In second-order nTS neurons recorded via patch clamp, network-driven spontaneous (s)EPSCs were not altered by OT and CRH after normoxia or CIH. Yet, after CIH but not normoxia, OTR-x and CRHR2-x reduced sEPSC amplitude, indicating tonic activation of these receptors maintains current amplitude. in normoxia afferent (TS)-EPSCs evoked at 0.5 and

20 Hz were not altered by OT and CRH or receptor blockers for OTR and CRHR2. However, CIH elevated TS-EPSCs in response to CRH and CRH+OT. Block of OTR and CRHR2 after CIH did not alter TS-EPSC amplitude, indicating their minimal tonic influence on sensory integration. Following the 20Hz stimulation, the peak of asynchronous activity increased in presence of CRH and the co-application with OT only after CIH. As a time control, in contrast to agonist or antagonist application, aCSF vehicle had no effect over the 40-min recording period. The expression of OT but not CRH fibers within the nTS decreased (immunohistochemistry) while OTR and CRHR2 mRNA increased (via RNA Scope). Altogether, our data show following CIH, nTS neuron sensitivity to OT and CRH is enhanced, which may contribute to the cardiorespiratory adaptions observed after CIH.

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Poster

PSTR093. Cardiovascular Regulation

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.06/DD27

Topic: F.06. Autonomic Regulation

Support: NIH grant R01HL147279

Title: Co-localization of oxytocin receptors and brainstem cardiac vagal neurons

Authors: X. WANG[1], C. RIBEIRO[1], ***D. MENDELOWITZ**[2];
[1]2300 Eye Street NW, Ross Hall, Rm 640, The George Washington University, SMHS, Washington, DC; [2]George Washington Univ., Washington, DC

Abstract: Surprisingly little is known about the expression of oxytocin (OXT) receptors in the nucleus ambiguus (NA) and dorsal motor nucleus of the vagus (DMNX), and in particular whether some, all, or none of the parasympathetic cardiac vagal neurons (CVNs) within these different nuclei express OXT receptors. In this study we characterized the co-localization of OXT receptors in CVNs, and non-CVN cholinergic neurons located in the NA and DMNX nuclei. The transgenic oxytocin receptor (OXTR)-Cre mouse JAX #031303 and the Cre dependent floxed ChR2-eYFP mouse JAX #012569 were crossbred for this study. Alexa Fluor 555 conjugates of cholera toxin subunit B was injected into the pericardial sac to retrogradely label CVNs. Colocalization analysis was performed using an Imaris algorithm for co-expression overlapped cells and the percentage of colocalization was calculated for each cell population. We found that over half of the CVNs in the DMNX co-localize with OXT receptor positive neurons. Surprisingly, CVNs in the NA, as well as the other ChAT neurons in the NA, have sparse co-localization with OXT receptor positive neurons. Future work is needed to test if selective activation of OXT receptor positive CVNs in the DMNX preferentially alters heart rate and/or

contractility, and more importantly, whether activation of OXT receptor positive CVNs prevents or reverses cardiovascular dysfunction in cardiorespiratory diseases.

Disclosures: **X. Wang:** None. **C. Ribeiro:** None. **D. Mendelowitz:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

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Topic: F.06. Autonomic Regulation

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Title: Dorsal motor vagal neurons can suppress heart rate and anxiety-like behavior in mice

Authors: *N. J. CONLEY, L. S. KAUFFMAN, P. CASTRO MARTINEZ, J. N. CAMPBELL; Univ. of Virginia Neurosci. Program, Charlottesville, VA

Abstract: The dorsal motor nucleus of the vagus (DMV) is a functionally heterogeneous region controlling digestive and metabolic functions through the vagus nerve but also innervating the heart, where its role in heart rate is less clear. We therefore chemogenetically activated DMV neurons in awake behaving mice while monitoring heart rate. To selectively activate DMV neurons, we injected an adeno-associated virus (AAV) expressing the excitatory chemogenetic receptor, hM3Dq only after recombination by both Cre and Flp recombinases, into the DMV of Chat-Cre::Phox2b-Flp mice. Of note, Chat and Phox2b are co-expressed by all DMV neurons but no surrounding neurons. We later intraperitoneally injected the hM3Dq ligand clozapine N-oxide (CNO; 1mg/kg) to activate hM3Dq+ DMV neurons while non-invasively measuring heart rate (ECGenie; n=2 females, 3 males; mean age ± S.D., 32 ± 2 weeks). We measured heart rate 20 minutes prior to CNO and 0, 20, 40 minutes and 1, 2, 6, 8, 24 hours later. CNO administration significantly but reversibly decreased heart rate by ~24% for approximately 6 hours, indicating that DMV neurons can suppress heart rate (mean ± standard deviation, SD: 20min before CNO, 705 ± 15 bpm; 40min after CNO, 536 ± 86 bpm, p=0.0271; 24hr after CNO, 727 ± 25 bpm, p=0.7347; one-way ANOVA, all timepoints, F1.660, 6.638=10.31; Dunnet's post-hoc test, p= 0.0107). Recent studies suggest that heart rate can alter anxiety levels, leading us to wonder whether the bradycardia we observed when activating DMV neurons was associated with a change in anxiety. We treated Chat-Cre::Phox2b-Flp mice (n=4 females, 4 males; mean age ± S.D., 45 ± 2 weeks) with CNO or vehicle and then measured anxiety-like behavior with an elevated plus maze. Activating DMV neurons with CNO significantly increased open arm exploration time, relative to vehicle, an effect which was abolished by co-administering the peripheral muscarinic antagonist methyl-atropine with CNO (mean ± SD: saline, 0.2 ± 0.6

seconds in open arm; CNO, 16.9 ± 13.7 seconds in open, p= 0.0212 vs. saline; CNO + methyl-atropine, 2.4 ± 3.4 seconds in open, p=0.0440 vs. CNO; one-way ANOVA, all timepoints, $F_{1.098, 7.688}$=9.471; Dunnet's post-hoc test, p= 0.0147). Histology confirmed that only DMV neurons expressed hM3Dq. Overall, our studies demonstrate that DMV neurons can suppress heart rate and decrease anxiety-like behavior and so highlight these neurons as a potential therapeutic target for treating heart disease and anxiety disorders.

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Poster

PSTR093. Cardiovascular Regulation

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Program #/Poster #: PSTR093.08/EE1

Topic: F.06. Autonomic Regulation

Support: FAPESP Grant 2022/06260-3 and 2020/11827-7
CNPq grant 304484/2022-9

Title: Control of contextual conditioned freezing behavior by medial prefrontal cortex is lateralized and unlinked to the cardiovascular regulation

Authors: *C. C. CRESTANI[1], L. GOMES-DE-SOUZA[2], A. SANTOS[2], C. BUSNARDO[2], R. L. NUNES-DE-SOUZA[2];
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Abstract: INTRODUCTION: The medial prefrontal cortex (mPFC) is a limbic structure involved in the expression of conditioned responses, including those related to contextual fear conditioning (CFC). A relevant aspect regarding the mPFC is the evidence of functional lateralization in the control of responses to aversive stimuli. In this sense, results from previous studies indicated that the right mPFC seems to be more directly related to the control of physiological and behavioral responses during stressful situations, while the left mPFC would have a counter-regulatory role by inhibiting the right mPFC. Despite this evidence, a possible lateralization in the control of contextual conditioned responses by the mPFC, especially the cardiovascular changes, has never been documented. **OBJECTIVE:** To investigate whether the control by the mPFC of expression of contextual conditioned responses is lateralized in male rats. **METHODS:** Male Wistar rats had cannula-guide implanted either bilaterally or in the right or left hemispheres of the mPFC. For the conditioning, each animal was placed individually in the conditioning chamber and received six shocks (1,5mA,3s). Twenty-four hours after the conditioning session, the animals were submitted to femoral artery cannulation surgery for cardiovascular recording. The fear retrieval test was performed 48 hours after the conditioning session. Independent set of animals received microinjections into either the left, the right or both

hemispheres (bilateral) of the mPFC of vehicle (saline, 100nL) or $CoCl_2$ (non-selective synaptic inhibitor) (1nmol/100nL) 10 min before the fear retrieval test. The blood pressure and heart rate increase and freezing response were evaluated during the fear retrieval test. **RESULTS:** Microinjection of $CoCl_2$either bilateral (t=2.60, P=0.0182) or into the right hemisphere (t=2.65, P=0.0192), but not into the left hemisphere (t=0.53, P=0.6021), of the mPFC decreased the freezing behavior. Bilateral pharmacological treatment of the mPFC also reduced the tachycardiac (t=2.89, P=0.0137), but not the pressor (t=1.3, P=0.2051), response during contextual fear retrieval. However, $CoCl_2$ administrated into either the right (pressor: P=0.4226; tachycardia: P=0.5889) or left (pressor: P=0.7493; tachycardia: P=0.2024) mPFC did not affect the cardiovascular changes. **CONCLUSIONS:** These results indicate that control of freezing behavior caused by contextual fear retrieval is lateralized in the mPFC (mediated mainly by the right hemisphere), whereas regulation of cardiovascular changes is mediated by pathways encompassing both hemispheres of the mPFC.

Disclosures: C.C. Crestani: None. **L. Gomes-de-Souza:** None. **A. Santos:** None. **C. Busnardo:** None. **R.L. Nunes-de-Souza:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.09/EE2

Topic: F.06. Autonomic Regulation

Support: NIH Grant R01DK117007
NIH Grant R01HL141393
NIH Grant 1F31HL164059-01

Title: Heterogeneous cellular senescence in the subfornical organ during angiotensin-II-induced hypertension

Authors: *S. A. DOW, H. ARESTAKESYAN, C. N. YOUNG;
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Abstract: Chronic uncontrolled hypertension is a global health concern, although the underlying contributing mechanisms remain unclear. Angiotensin-II (Ang-II) is a well-recognized driver of hypertension, particularly through its actions in the central nervous system to promote sympathoexcitation. However, as a peptide hormone, Ang-II is too large to cross into the brain and acts at circumventricular regions lacking a blood-brain-barrier, notably the subfornical organ (SFO). Ang-II induces pro-hypertensive cellular stressors (e.g. oxidative stress, inflammation, endoplasmic reticulum stress) in the SFO, but how these stress pathways lead to long-term changes in cellular function remains unclear. Importantly, chronic activation of stress pathways can induce cellular senescence. Chronic senescence leads to detrimental changes in cell

metabolism, macromolecule damage, and a pro-inflammatory environment capable of propagating senescence, known as the senescence-associated secretory phenotype (SASP). Thus, we hypothesized that Ang-II would elicit cellular senescence in the SFO. To test this, male C57Bl/6J mice were implanted with subcutaneous osmotic minipumps for chronic infusion of Ang-II (600 ng/kg/min) for 0 or 14 days (n=4-5/group). Using micropunches of the SFO, robust mRNA increases in key senescence indicators *p16* (1.96±0.23 fold Day 0, $p<0.05$) and *p21* (2.63±0.52 fold Day 0, $p<0.05$) were observed after 14 days of Ang-II infusion. This was paralleled by elevations in inflammatory SASP markers (e.g. *IL-6*: 2.06±0.14 fold Day 0; *IL-10*: 2.07±0.34 fold Day 0, both $p<0.05$). Immunohistochemical analysis further revealed a marked increase in p16 (Integrated density: 1.46±0.24 fold Day 0, $p=0.07$) and p21 expression (Integrated density: 1.15±0.09 fold Day 0, $p=0.05$) throughout the rostral to caudal extent of the SFO in response to Ang-II infusion. We next aimed to characterize the SFO cell types affected by Ang-II-induced senescence. When examining neuronal populations with double immunohistochemistry, extremely low to no colocalization with p16 was found with neurons [p16/NeuN: Mander's overlap coefficient (MOC)=0.08±0.01]. However, p16 was highly colocalized with astrocytes (p16/GFAP: MOC=0.98±0.01). In contrast, p21 moderately colocalized with both neurons (p21/NeuN: MOC=0.26±0.02) and astrocytes (p21/GFAP: MOC=0.45±0.03). These findings indicate that: 1) Ang-II induces cellular senescence and SASP in the SFO during hypertension development; and 2) p16 and p21-associated senescence in response to Ang-II occurs in various SFO cell types.

Disclosures: S.A. Dow: None. **H. Arestakesyan:** None. **C.N. Young:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.10/EE3

Topic: F.06. Autonomic Regulation

Support: T32 DK007690
AHA Award Number 834962
T32 DK112751

Title: Neuroanatomical Substrate of Neurocircuitry Couples in Cardiovascular and Metabolic Control by the Central Autonomic System

Authors: *P. A. WILLIAMS[1,2], D.-F. GUO[1,2], A. OLSON[1], K. RAHMOUNI[1,3,2];
[1]Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA; [2]Iowa VA Hlth. Care Syst., Iowa City, IA; [3]Intrnl. Med., Carver Med. College, Univ. of Iowa, Iowa City, IA

Abstract: The autonomic networks of the central nervous system (CNS) play an important role in the regulation of many physiological functions. Obesity is often associated with hypertension which is a serious medical condition that increase mortality. Therefore, obesity-induced

hypertension may be the consequence of a cardiovascular-metabolic coupling in the CNS autonomic network. We and others have previously shown the existence of shared nuclei in the autonomic networks innervating organs such as the kidney, liver, and brown adipose tissue (BAT). However, whether there are shared neurons within these nuclei associated with these three organs is unknown. To address this, two groups of mice received injections of pseudorabies virus (PRV) expressing a green fluorescent protein (GFP) into both kidneys and PRV expressing a red fluorescent protein (RFP) in either the interscapular BAT (iBAT) or the left lobe of the liver. The animals were sacrificed 5-7 days post-injection and perfused. The brains were extracted, sectioned at 50 μm thickness, stained, and imaged with confocal microscopy. Sections were matched to the mouse brain atlas (Franklin & Paxinos) and neurons co-expressing GFP and RFP throughout the brain were identified. In addition, soma morphology was measured using ImageJ software. We found several nuclei in which neurons were co-labeled with GFP (kidney) and RFP (BAT or liver). Co-expressing neurons were observed in areas such as the cortical regions (motor cortex and amygdala), hypothalamus (paraventricular nucleus (PVN), lateral hypothalamus (LH), and dorsomedial hypothalamus (DMH)), midbrain regions such as the periaqueductal gray, and brainstem nuclei such as the locus coeruleus (LC). In general, there appeared to be two scenarios for shared nuclei: 1) in regions such as LH, nucleus of the solitary tract, and dorsal motor nucleus of vagus there was little to very little co-expression, and 2) in regions such as PVN, DMH, LC, and motor cortex there was moderate to high levels of co-expression. Distribution of soma size demonstrated differences between regions and organs. Comparing the kidney and iBAT soma sizes using the Kolmogorov-Smirnov test suggested that for the PVN, motor cortex, and LC the two distributions were statistically different ($p<0.05$), but not for the LH ($p>0.1$). This is the first study to provide anatomical evidence for potential coupling between the autonomic networks regulating cardiovascular and metabolic functions. Moreover, our data demonstrate that although there is overlap of neurons in diverse nuclei there may also be a difference in morphological phenotype in these nuclei associated with cardiovascular and metabolic functions.

Disclosures: **P.A. Williams:** None. **D. Guo:** None. **A. Olson:** None. **K. Rahmouni:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.11/EE4

Topic: F.06. Autonomic Regulation

Support: Warren Alpert Distinguished Scholar to LHN
BWF - CASI to LHN
Branco Weiss fellowship to LHN
Life Sciences Research Foundation fellowship to LHN

Title: Developmental Landmarks of Motor Parasympathetic Circuits for Cardiac Control in Zebrafish

Authors: *M. PHILLIPS, K. SHI, L. HERNANDEZ-NUNEZ;
Mol. and Cell. Biol., Harvard Univ., Cambridge, MA

Abstract: Developmental Landmarks of Motor Parasympathetic Circuits for Cardiac Control in Zebrafish Morgan Phillips*, Keyue Shi*, Luis Hernandez-Nunez#*Equal contributions# Senior authorResearch in the field of systems neuroscience in the past decade has primarily focused on explaining behavioral dynamics as a function of brain activity. This approach ignores other system components, such as internal organs and the autonomic nervous system. Through the autonomic nervous system, viscera can modulate and be modulated by brain activity. Consequently, it is important to establish the circuit mechanisms that underlie brain-organ interactions. To construct a clear model of system-level processing that incorporates the autonomic and central nervous systems, we need to conduct functional single-cell resolution imaging and perturbation of both systems. The only vertebrate model organism in which this process is feasible is the zebrafish larvae. In this study, we focused on the development of the parasympathetic circuits, part of the autonomic system, that control the heart. Using anatomical imaging, we established developmental landmarks for parasympathetic innervation of the heart. We then combined calcium imaging and optogenetics to determine the physiological role of the motor parasympathetic neurons associated with the heart.

Disclosures: M. Phillips: None. **K. Shi:** None. **L. Hernandez-Nunez:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.12/EE5

Topic: F.06. Autonomic Regulation

Support: NIH U19NS104653 to FE and MF
Life Sciences Research Foundation fellowship to LHN
Warren Alpert Distinguished Scholar award to LHN
Burroughs Wellcome Fund Career Award at the Scientific Interface to LHN

Title: Functional Development of Heart-Brain Feedback Control Neural Circuits

Authors: *L. HERNANDEZ-NUNEZ[1], A. MARKARIAN[1], K. SHI[1], J. AVRAMI[1], M. C. FISHMAN[2], F. ENGERT[1];
[2]Stem Cell and Regenerative Biol., [1]Harvard Univ., Cambridge, MA

Abstract: Autonomic control of cardiac function is essential for survival, yet the functional diversity of the autonomic sensory and motor circuits of the heart remains poorly understood. Here we take a multidisciplinary approach, combining systems neuroscience techniques, genetics, and control theory to study the role of autonomic sensory and motor circuits in larval zebrafish. While larval zebrafish's optic and genetic accessibility has made it a popular choice

for studying how the brain processes environmental cues to modulate behavior, it has not yet been used to study organ control or the autonomic nervous system (ANS) from a systems neuroscience perspective. Thus, we use calcium imaging, optogenetics, pharmacology, and electron microscopy to map the developmental time course of anatomical and functional innervation of the heart. We identify the emergence of parasympathetic and sympathetic control of the heart, as well as the anatomically defined neural populations needed for heart modulation. We also show the onset of cardiac sensing and cardiac state feedback to the brain. Our study provides a timeline of developmental landmarks of the autonomic circuits for heart control and sets the stage for future mechanistic studies of neurocardiac circuits.

Disclosures: L. Hernandez-Nunez: None. **A. Markarian:** None. **K. Shi:** None. **J. Avrami:** None. **M.C. Fishman:** None. **F. Engert:** None.

Poster

PSTR093. Cardiovascular Regulation

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Topic: F.06. Autonomic Regulation

Support: FAPESP 2015/23467-7
FAPESP 2020/10180-0
CNPq

Title: Sympathetic and angiotensinergic activity in spontaneously hypertensive rats treated with 3-amino-1,2,4-triazole

Authors: R. B. PONTES, D. S. A. COLOMBARI, P. M. DE PAULA, E. COLOMBARI, C. A. F. ANDRADE, L. A. DE LUCA, Jr, *J. V. MENANI;
Physiol. and Pathology, UNESP, Araraquara, Brazil

Abstract: Previous studies from our laboratory have shown that the pressor response to intracerebroventricular (icv) administered angiotensin II (ANG II) in normotensive rats or spontaneously hypertensive rats (SHRs) is attenuated by increased central H_2O_2 concentration, produced either by direct H_2O_2 icv injection or by increased endogenous H_2O_2 centrally in response to local catalase inhibition with 3-amino-1,2,4-triazole (ATZ). In the present study, we evaluated the effects of ATZ administered peripherally on arterial pressure and sympathetic and angiotensinergic activity in SHRs. Male SHRs weighing 280-330 g were used. Mean arterial pressure (MAP) and heart rate (HR) were recorded in conscious freely moving SHRs. Acute intravenous injection of ATZ (300 mg/kg of body weight) did not modify MAP and HR during the next 4 h, however, the treatment with ATZ (300 mg/kg of body weight twice per day) for 3 days reduced MAP (144 ± 6, vs. saline: 183 ± 13 mmHg), without changing HR. Intravenous hexamethonium (ganglionic blocker) produced a smaller decrease in MAP 4 h after ATZ (-25 ± 3, vs saline -38 ± 4 mmHg). Losartan (angiotensinergic AT_1 receptor blocker) produced a

significant depressor response 4 h after ATZ (-22 ± 4, vs. saline: -2 ± 4 mmHg) and in 3-day ATZ treated SHRs (-25 ± 5, vs. saline: -9 ± 4 mmHg). The results suggest that the treatment with ATZ reduces sympathetic activity in SHRs and simultaneously increases angiotensinergic activity.

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Poster

PSTR093. Cardiovascular Regulation

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Program #/Poster #: PSTR093.14/EE7

Topic: F.06. Autonomic Regulation

Support: FONDECYT 11220962
FONDECYT 1220950

Title: Altered cardiorespiratory function in APP/PS1 double transgenic mice: Role of brainstem pre-sympathetic motor neurons on Alzheimer's disease progression

Authors: *C. TOLEDO[1], K. G. SCHWARZ[2], A. R. ALVAREZ[2], N. INESTROSA[3], R. DEL RIO[2];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline. While therapeutic approaches targeting neurodegenerative mechanism associated with cognitive impairment have been extensively explored, other comorbidities including cardiorespiratory abnormalities have not been thoroughly investigated. Notably, sleep-disordered breathing and autonomic dysfunction are both closely linked to poor prognosis in AD pathology. In preliminary studies, we showed an increase neural activity from pre-sympathetic motor neurons located in the rostral ventrolateral medulla region (RVLM-C1), a main region involved in cardiorespiratory regulation, in experimental AD. Hence, in the present study we aimed to determine the role of RVLM-C1 neurons on autonomic and sleep-disordered breathing in APP/PS1 double transgenic mice, an experimental model showing AD-like pathology. Whole-body plethysmography and blood pressure monitoring in freely moving mice were used to study sleep-associated cardiorespiratory disorders. The Morris water maze was used to evaluate spatial learning and memory. Bilateral stereotaxic injections of anti-dopamine β-hydroxylase-saporin (DβH-SAP) into the RVLM was used to selectively destroy C1 neurons. Compared to wild type (WT), APP/PS1 mice displayed sympatho-excitation (ΔHR: -80±5 vs -125±10, WT vs APP/PS1, respectively), a higher incidence of cardiac arrhythmias (events/h 6.0±1.0 vs 12±1.5, WT vs APP/PS1, respectively), and sleep-disordered breathing (AHI: 8.5±2.0

vs 18.0±3.0, WT vs APP/PS1, respectively). Partial ablation of RVLM-C1 neurons (~70%) in APP/PS1 mice results in two-fold and tree-fold reduction in cardiac sympathetic drive and arrhythmogenesis, respectively. Furthermore, APP/PS1 mice treated with DβH-SAP showed marked improvements in breathing regularity (IS: 7.9±1.1 vs 16.9±2.2, APP/PS1$_{DβH\text{-}SAP}$ vs APP/PS1, respectively) and a restoration of normal sleep efficiency (SE: 75.5±4.3 vs 58.1±6.4, APP/PS1$_{DβH\text{-}SAP}$ vs APP/PS1, respectively) compared to untreated APP/PS1 mice. Finally, we found that ablation of RVLM-C1 neurons significantly improve cognitive performance in APP/PS1 mice. Our results shows that RVLM-C1 neurons play a main role in the development/maintenance of cardiorespiratory disorders in experimental AD

Disclosures: C. Toledo: None. **K.G. Schwarz:** None. **A.R. Alvarez:** None. **N. Inestrosa:** None. **R. Del Rio:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.15/EE8

Topic: F.06. Autonomic Regulation

Title: Impact of some limbic structures on evoked activity of the vagus sensitive neurons of the solitary tract nucleus

Authors: *N. BEHNAM DEHKORDI, E. AVETISYAN, A. PETROSYAN, N. SARGSYAN, V. SARKISIAN;
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Abstract: Impact of some limbic structures on evoked activity of the vagus sensitive neurons of the solitary tract nucleus *N.B.DEHKORDI, E.A.AETISYAN, A.A.PETROSYAN, N.V.SARGYAN, V.H.SARKISIAN Orbeli Inst.of fhysiology, NAS of Armenia. **Disclosures** N.B.DEHKORD: none**.** E.A.AETISYAN: none A.A.PETROSYAN: none N.V.SARGYAN: none V.H.SARKISIAN: none **Abstract** Elucidation of the mechanisms of regulation and control of autonomic reactions (cardiovascular, vasomotor, respiratory, etc.) by the structures of the limbic brain is important for the correct diagnosis of diseases, associated with the pathology of the aforesaid systems. The limbic system, receiving afferent signals from almost all internal organs, itself affects the neurons of the solitary tract (NST), which is the terminal zone of the laryngeal, tracheobronchial, pulmonary, cardiac and gastrointestinal afferent fibers of the vagus nerve. In order to clarify all these issues, we selected the structures of the limbic brain - the paraventricular nucleus of the hypothalamus (PVN), the corticomedial nucleus (CMN) of the amygdala and the dorsal limbic cortex (DLC), which not only have direct access to the studied vagosolitary neurons, but also take an active part in the cardiovascular reactions. In vivo electrophysiological experiments were performed on anesthetized albino Wistar rats (220-240 g). The experimental protocol corresponded to the conditions of the European Communities Council Directive (2010/63/UE). Functional identification of input vagosensitive neurons was

carried out with stimulation of the vagus nerve in the cervical region. 42 NST neurons were recorded, of which 25 (59.5%) units responded to a single stimulation of the PVN by initial excitation and of which 15 responded with a short latency (4-8 ms), 8 - with average values of (10- 20ms) and two neurons with - 30-40ms. The remaining 17 vagal units were unresponsive to stimulation. The recovery cycle of test responses for the majority of neurons (55%) is more than 20ms, 17% - up to 20ms and 28% - up to 10ms. When stimulation of CMN a wide range of latentcies of phase-excitatory reactions was revealed - 5-10ms (35.7%), 11-19ms 46.4%), 20-40ms (17.9%), which indicates the presence of various implementation stages of amygdalo-fugal discharges. A strong blocking effect of DLK on the input "vagal" NST neurons was found, starting from 10 to 600 ms. Thus, the studied brain structures play a significant role in the mechanisms of control of the activity of vago-sensitive NST neurons and provides not only the implementation of vago-vagal reflexes, but also take an active part in the mechanism of central regulation of the activity of the body.visceral systems

Disclosures: N. Behnam Dehkordi: None. **E. Avetisyan:** None. **A. Petrosyan:** None. **N. Sargsyan:** None. **V. Sarkisian:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.16/EE9

Topic: F.06. Autonomic Regulation

Support: R01HL154512

Title: Dna hypomethylation promotes agtr1a and slc12a2 transcription in the hypothalamus of spontaneously hypertensive rats

Authors: *K. GHOSH, J.-J. ZHOU, J.-Y. SHAO, S.-R. CHEN, H.-L. PAN;
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Abstract: Increased expression of the angiotensin AT1 receptor (encoded by *Agtr1a*) and Na^+-K^+-Cl^- cotransporter-1 (NKCC1, encoded by *Slc12a2*) in the hypothalamic paraventricular nucleus (PVN) contributes to elevated sympathetic outflow in hypertension. However, little is known about mechanisms underlying transcriptional activation of *Agtr1a* and *Slc12a2* in the PVN in hypertension. DNA methylation is a critical epigenetic mechanism that regulates gene expression. In this study, we determined whether DNA methylation mediates upregulation of AT1 and NKCC1 in the PVN in spontaneously hypertensive rats (SHR), a genetic model of hypertension. Methylated DNA immunoprecipitation and bisulfite sequencing PCR revealed that CpG methylation at *Agtr1a* and *Slc12a2* promoters in the PVN was diminished in adult SHR compared with normotensive Wister Kyoto rats (WKY). Chromatin immunoprecipitation-qPCR showed that the enrichment of DNA methyltransferases and MECP2, a DNA methylation reader protein, at *Agtr1a* and *Slc12a2* promoters in the PVN was profoundly reduced in SHR compared

with WKY. By contrast, the enrichment of TET1, a DNA demethylase, at *Agtr1a* and *Slc12a2* promoters in the PVN was significantly greater in SHR than in WKY. Furthermore, microinjecting of RG108, a DNMT inhibitor, into the PVN of WKY increased arterial blood pressure and augmented correspondingly *Agtr1a* and *Slc12a2* mRNA levels in the PVN. Conversely, microinjection of C35, a specific TET inhibitor, into the PVN of SHR markedly reduced arterial blood pressure with concurrent reduction in *Agtr1a* and *Slc12a2* mRNA levels in the PVN. Collectively, these findings suggest that upregulation of AT1 and NKCC1 in the PVN in hypertension results from DNA hypomethylation.

Disclosures: K. Ghosh: None. **J. Zhou:** None. **J. Shao:** None. **S. Chen:** None. **H. Pan:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.17/EE10

Topic: F.06. Autonomic Regulation

Support: NIH grant HL154512

Title: Calcineurin controls synaptic AMPA receptor phenotypes of hypothalamic presympathetic neurons via GluA1/GluA2 phosphorylation and α2δ-1

Authors: *J.-J. ZHOU, J.-Y. SHAO, S.-R. CHEN, H.-L. PAN;
The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Hypertension is a prominent side effect of calcineurin inhibitors, such as tacrolimus (FK506) and cyclosporine, used clinically as immunosuppressants. Calcineurin inhibitor-induced hypertension is associated with augmented sympathetic output sustained by glutamatergic input in the hypothalamic paraventricular nucleus (PVN). Synaptic AMPA receptors (AMPARs) and their subunit composition are dynamically regulated in the PVN. In this study, we found that systemic treatment with FK506 in rats profoundly increased serine-phosphorylation of GluA1 and GluA2 in hypothalamic synaptosomes. Co-immunoprecipitation (co-IP) analysis showed that FK506 treatment significantly reduced synaptic GluA1/GluA2 heteromers in the PVN. Whole-cell patch-clamp recordings in brain slices showed that FK506 treatment shifted the current-voltage relationship of AMPAR-mediated excitatory postsynaptic currents (AMPAR-EPSCs) from linear to inward rectification in retrogradely labeled, spinally projecting PVN neurons. IEM-1460, a specific calcium permeable-AMPARs (CP-AMPARs) blocker, induced a larger reduction of AMPAR-EPSCs in labeled PVN neurons in FK506-treated rats than in vehicle-treated rats. Furthermore, FK506 treatment significantly increased the interaction of α2δ-1 with GluA1 and GluA2 in the PVN. Inhibiting α2δ-1 with gabapentin or disrupting α2δ-1-AMPAR interactions with an α2δ-1 C terminus peptide restored the amount of synaptic GluA1/GluA2 heteromers in the PVN and diminished inward rectification of AMPAR-EPSCs in labeled PVN neurons from FK506-treated rats. In addition, microinjection of IEM-1460 or α2δ-1 C terminus

peptide into the PVN significantly reduced renal sympathetic nerve discharges and arterial blood pressure in FK506-treated rats but had no such effect in vehicle-treated rats. These findings suggest that calcineurin constitutively controls the phenotype of synaptic AMPARs via regulating phosphorylation of GluA1/GluA2 subunits and their interaction with α2δ-1 in the hypothalamus. The increased prevalence of synaptic CP-AMPARs in PVN presympathetic neurons contributes to augmented sympathetic outflow in calcineurin inhibitor-induced hypertension.

Disclosures: **J. Zhou:** None. **J. Shao:** None. **S. Chen:** None. **H. Pan:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.18/Web Only

Topic: F.06. Autonomic Regulation

Title: Sensitivity of arterial baroreflex as a prognostic marker in determining the properties of vegetotropic compounds

Authors: *V. SARKISIAN, E. AVETISYAN, A. PETROSYAN, M. SHIRINYAN;
Orbeli Inst. Physiol, Yerevan, Armenia

Abstract: Sensitivity of arterial baroreflex as a prognostic marker in determining the properties of vegetotropic compounds*V.H.Sarkisian[1], E.A.Avetisyan[1], A.A. Petrosyan[1], M.E. Shirinyan[21]Orbeli Institute of Physiology, NAS of Armenia [2]Scientific Technological Center of Organic and Pharmaceutical Chemistry, NAS of ArmeniaThe development of a new antihypertensive drug is a laborious process aimed at studying the mechanism of action and pharmacological effects of the test compound. It seems appropriate to create combined models, such as *in vivo & in silico*, in order to identify a greater number of pharmacological effects of the developed drug with less resource intensity. For the development of antihypertensive drugs, the arterial baroreflex (ABR) was chosen as a test target and a simulated system.The studies were carried out on 9 series (1 control and 8 experimental groups, total sample n=60) of anesthetized white rats (240-270 g). Sensitivity of ABR (SBR) was assessed by the Oxford method against the background of a single injection (i.v.) of the following vegetotropic drugs: non-selective β-blocker (β-B) propranolol (0.5 and 2 mg/kg), selective α2-B idazoxane (1 mg/kg) and developed in Armenia non-selective β-A with fobufol (0.5 and 2 mg/kg), α2-A beditin (3 and 15 mg/kg), ganglioplegic gangleron (3 mg/kg). Phenylephrine (PE) at a dose of 15 μg/kg (iv) was chosen as a vasoconstrictor.During the Oxford test, against the background of β-blockers, there was a tendency to reduce the depth of bradycardia in the range [15″÷30″] with an increase in their β-adrenergic blocking (AB) activity and in the range [0″÷10″] in the presence of membrane stabilizing properties. An unequal hypertensive response to PE was recorded with different reactivity of the selected drugs to vascular α1-adrenergic receptors (α1-AR) and presynaptic α2-AR. There was an increase in SBR compared with the control group against the background of

ganglerone and, to varying degrees, a decrease in SBR against the background of other drugs. Against the background of fobufol at a dose of 0.5 mg/kg, the hypertensive response was not accompanied by changes in heart rate in [0"÷30"]. SBR against the background of fobufol (0.5 mg/kg) was determined by extrapolation of the experimental data of the remaining 8 groups of animals. Using the same method, a model for predicting the membrane-stabilizing properties of β-B was developed.It is proposed to take into account differences in the impact effect of known antihypertensive drugs on hypertensive and chronotropic reactions in the Oxford ABR testing in predictive models when studying the properties of new vegetotropic drugs.

Disclosures: V. Sarkisian: None. **E. Avetisyan:** None. **A. Petrosyan:** None. **M. Shirinyan:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.19/EE11

Topic: F.06. Autonomic Regulation

Support: RF1 MH122886

Title: Parasympathetic Arousal Circuitry Supports Cognitive Ability in Normal Blood Pressure and Hypertensive Individuals

Authors: *A. D. BARBER[1,2], J. R. JENNINGS[3];
[1]Psychiatry, Feinstein Inst. for Med. Res., Manhasset, NY; [2]Psychiatry, Zucker Sch. of Med. at Hofstra/Northwell, Hempstead, NY; [3]Psychiatry, Univ. of Pittsburgh Med. Ctr., Pittsburgh, PA

Abstract: Parasympathetic arousal-related task fMRI activity is found in widespread cortical and thalamic circuits and relates to cognitive efficiency (RT*Error Rate). Parasympathetic activity originates in the Nucleus of the Tractus Solitarius (NTS), the brainstem region that is directly connected to the heart through the baroreflex. Baroreflex sensitivity is reduced in hypertensive individuals and it is unknown whether parasympathetic activity occurs in hypertension: whether it is supported by the same brain circuits, or whether it also relates to cognitive ability.
The current study examined parasympathetic arousal-related task fMRI activity in the Human Connectome Project-Young Adult dataset during the Working Memory Task. 406 participants had usable fMRI and pulse oximetry data and were either classified as normal blood pressure (n=242) or hypertensive (n=164). Those with elevated blood pressure, who did not qualify as hypertensive, were excluded. Cardiac-BOLD activity was identified using on-going in-scanner heartrate measured by pulse oximetry during the Working Memory Task fMRI session based on our previous approach. Cardiac-BOLD activity was compared between the two groups and was related to individual differences in parasympathetic heart rate variability (HRV: natural log of the High Frequency Power) and cognitive efficiency. Group models included covariates for: sex, age, framewise displacement (FD), and proportion of volumes with FD>0.3. All contrasts were

thresholded at a voxel-wise $p<0.001$ and cluster-wise $p<0.05$.
Widespread parasympathetic arousal-related brain activity occurred in cortical and thalamic regions. Cortical activity was robust across visual and higher order cognitive networks. Activity did not differ in the hypertension group; however, when individual differences in parasympathetic HRV were examined, differences between the two groups emerged. In both groups, cardiac-BOLD fMRI activity was robustly related to parasympathetic HRV in the NTS as well as in extensive thalamic and cortical regions. This relationship was significantly stronger in the normal blood pressure than hypertensive group across an extensive set of brainstem, thalamic, and cortical regions. Relationships with cognition echoed those of parasympathetic HRV, with associations found in brainstem, thalamic, and cortical regions in both groups, but stronger associations in the normal blood pressure group.
The findings support the role of parasympathetic arousal circuits in cognitive abilities. Altered activity in these circuits is found in hypertensive individuals and is consistent with NTS and baroreflex circuitry.

Disclosures: A.D. Barber: None. **J.R. Jennings:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.20/EE12

Topic: F.06. Autonomic Regulation

Support: NSF GRFP Fellowship (Lia Chen)

Title: Associations of systolic blood pressure, diastolic blood pressure, and higher order cognition across functional neuroimaging paradigms

Authors: *L. CHEN, E. B. RILEY, A. K. ANDERSON, E. DE ROSA;
Psychology, Cornell Univ., Ithaca, NY

Abstract: A lifespan sample of 61 adults (M = 44.56, SD = 21.49, range = 18 to 87 years) participated in this Internal Review Board approved study. In our fMRI design, young and older adults were tasked to exercise selective attention by judging the sex of non-expressive face images that were superimposed with place images. Intermixed in the design was a working memory task, where they responded to n-back items, indicating whether a given target face was recently presented during the selective attention task.
Group-level neural contrasts were performed via BOLD fMRI analysis, revealing significant age-related differences and interactions in brain-level substrates during selective attention and working memory trials. In healthy older adults, executive declines in working memory were linked to increased brain-level activations in the precuneus, middle frontal gyrus, and fusiform gyrus 3 (FG3)/parahippocampal place area (PPA), despite only the face being shown for the working memory probe. In older adults, this was additionally supported by differentially greater

activation in the dorsal striatum, with clustering in the caudate nucleus.
In addition to performing the intermixed selective attention and working memory task, participants completed a series of physiological tests measuring central (carotid artery) and brachial blood pressure. Utilizing a multivariate general linear model (GLM), analyses of cognition, baseline systolic blood pressure, and baseline diastolic blood pressure revealed significant correlations between task-active selective attention and central systolic blood pressure ($r = -.12$, $p < .01$), brachial systolic blood pressure ($r = -.33$, $p < .01$) , and brachial diastolic blood pressure ($r = -.35$, $p < .01$).
We further found that elevations in systolic and diastolic blood pressure were strongly associated with poorer working memory performance. Specifically, 1-back working memory performance was negatively correlated with central systolic blood pressure ($r = -.28$, $p < .01$), brachial systolic blood pressure ($r = -.44$, $p < .001$), and brachial diastolic blood pressure ($r = -.47$, $p < .001$). 2-back working memory was correlated with central systolic blood pressure ($r = -.10$, $p < .01$), brachial systolic blood pressure ($r = -.33$, $p < .01$), and brachial diastolic blood pressure ($r = -.35$, $p < .001$). Furthermore, we discovered that this association of heightened blood pressure levels and declined selective attention and working memory performance was not selective for older age levels, but rather across the full lifespan. Controlling for baseline blood pressure differences across aging substantially diminished age-related differences in executive function.

Disclosures: L. Chen: None. **E.B. Riley:** None. **A.K. Anderson:** None. **E. De Rosa:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.21/EE13

Topic: F.06. Autonomic Regulation

Title: Acute effects of high-intensity interval exercise versus moderate-intensity exercise on executive function and autonomic nervous activities in older adults

Authors: J.-P. CHANG[1], C.-W. YEN[2], Y.-J. CHANG[3], ***M. HSU**[4];
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Abstract: Background: Physical exercise has been recognized as a preventive measure against cognitive decline in older adults, with potential involvement of autonomic nervous system function. However, the impact of different exercise modes, particularly high-intensity interval exercise (HIIE), on cognitive performance remains insufficiently investigated. This study aimed to compare the immediate effects of two aerobic exercise modes, HIIE and moderate-intensity exercise (MIE), on executive function and autonomic nervous activities in older adults. Methods: Twenty-eight community-dwelling older adults (age: 67.5±2.41years) were recruited. Each

participant randomly underwent three conditions (watching a cycling exercise video, HIIE leg cycling, and continuous MIE leg cycling) on different days within two weeks. The HIIE mode was set at alternating with 70% and 30% heart rate reserve (HRR) for 2 minutes each for a total of 20 minutes. The MIE was at 50%HRR for 20 minutes. Executive function and autonomic nervous activities were measured immediately, 30 minutes, and 60 minutes after exercise. Executive function assessments included Stroop task, digit span, and visual elevator. Heart rate variability (HRV) was used to evaluate autonomic nervous activities. The two-way repeated measures ANOVA was used to compare the three conditions on executive function tests and HRV over time. Results: Intervention mode did not significantly influence any HRV parameter, the Stroop task ($p>0.05$) and visual elevator test, and the total score and error rate of digit span test. Though no significant differences between the interventions, the reaction time of digit span test was significantly improved in HIIE, even at 60 mins after exercise. The SDNN (standard deviation of normal-to-normal intervals) was significantly increased after watching the exercise video. Conclusion: It appears that HIIE and MIE induce similar immediate responses on executive function and autonomic nervous activities in older adults.

Disclosures: **J. Chang:** None. **C. Yen:** None. **Y. Chang:** None. **M. Hsu:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.22/EE14

Topic: F.06. Autonomic Regulation

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The William K. Warren Foundation
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The Union Nationale de Familles et Amis de Personnes Malades et Handicapées Psychiques (UNAFAM)

Title: Dynamic Brain Responses to Perturbation of Cardiac Interoception: An EEG-fMRI Study of Heartbeat Evoked Potentials

Authors: *C. VERDONK[1,2], A. R. TEED[1], E. J. WHITE[1], X. REN[1], J. L. STEWART[1,3], M. P. PAULUS[1,3], S. S. KHALSA[1,3];
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Abstract: Characterizing dynamic brain responses to cardiovascular perturbations is of key importance to understanding neural mechanisms driving the processing of interoceptive signals. Here we examined whether the peripheral adrenergic modulation of cardiovascular signals

differentially affects the heartbeat evoked potential (HEP), a neural marker of brain activity in response to heartbeats, during concurrent electroencephalogram and functional magnetic resonance imaging (EEG-fMRI) scanning. Data were collected in 24 healthy females during the administration of intravenous bolus infusions of isoproterenol (0.5 and 2.0 μg), a rapidly acting peripheral beta-adrenergic agonist akin to adrenaline resulting in increased cardiovascular signals, and saline, each administered twice in a double-blind fashion within a single scanning session. We minimized cardiac-related artifacts contaminating the EEG signal using a combination of the optimal basis set approach and independent component analysis. HEP data was subjected to cluster-based permutation testing to compare HEP amplitudes during isoproterenol and saline within the 0 to 600 ms time range after the cardiac R-wave event, and to assess their association with blood oxygenation level dependent (BOLD) whole-brain fMRI responses. Adrenergic stimulation significantly modulated the HEP, with larger amplitudes at left parietal locations between 360 and 528 ms after the R-wave event (Monte-Carlo $p<0.03$, Cohen's $d>0.57$). However, HEP amplitudes showed substantial fluctuations at the individual level across repeated baseline measures at frontocentral electrodes in the latency range of 236-312 ms after the R-wave event (Monte-Carlo $p=0.04$, Cohen's $d=0.22$). BOLD fMRI signals in the bilateral insula during the 2 μg isoproterenol infusion correlated significantly with HEP amplitude within a 148 ms window from 248 to 396 ms after the cardiac R-wave event ($r=-0.75$, Monte-Carlo $p=0.001$), but not with activation of the ventromedial prefrontal and the parieto-temporal cortices. These findings show that the HEP is an electrophysiological measure capable of dynamically reflecting changes in peripheral cardiovascular status and activation in the insula during adrenergic stimulation, indicating its utility in characterizing neural responses to interoceptive signals. However, given the variability observed in HEP signals at baseline, future research should include signal correction measures. This approach is suitable for guiding future studies of heart-brain communication, including those focused on characterizing the amplified interoceptive awareness of cardiac signals seen in anxiety disorders.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.23/EE16

Topic: F.06. Autonomic Regulation

Support: MES Grant A/249

Title: Increased sympathetic activity and anxiety in long COVID

Authors: *B. LKHAGVASUREN[1], E. TUMURBAATAR[2], E. BAT-ERDENE[3], C. ERDENEBAATAR[4], M. LKHAGVASUREN[2], B. SELENGE[2], T. JADAMBA[2]; [1]Psychosomatic Med., Mongolian Neurosci. Society, Ulaanbaatar, Mongolia; [2]Brain and Mind Res. Institute, Mongolian Acad. of Sci., Ulaanbaatar, Mongolia; [3]Child Hlth. Inst., New Brunswick, NJ; [4]Brain and Mind Res. Inst., Ulaanbaatar, Mongolia

Abstract: Background: The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has resulted in a global healthcare crisis with significant impacts on individuals' health and well-being. Beyond the acute phase of COVID-19, a subset of patients continues to experience persistent symptoms and complications, a condition commonly referred to as long COVID or post-COVID-19 fatigue syndrome (PVFS). However, the cause of this mechanism remains unknown, and there has been limited research conducted on the general population. Thus, our aim was to investigate the autonomic dysfunctions in individuals with PVFS in the general population. Methods: This population-based cross-sectional study was carried out in the general population of Ulaanbaatar in 2023. After physical examination, trained researchers applied structured interviews to diagnose PVFS, followed by a recording of heart rate variability to detect autonomic dysfunctions. Psychological factors and the quality of life were measured using the Hospital Anxiety Depression Scale (HADS), the Pittsburgh Sleep Quality Index, and the World Health Organization Quality of Life-Brief. Binary logistic regression was used to examine the effects of risk factors on the associations between long COVID and autonomic dysfunctions. Results: Among participants (n=398, mean age = 33.6±8.2 years), a total of 21 (5.3%) participants met the Fukuda diagnostic criteria for PVFS. Gender, residency location, hand grip strength, anxiety score, and quality of life were different between the participants with and without PVFS. LF/HF (ratio of low-frequency to high frequency), the index of sympathovagal balance, was correlated with HADS anxiety. Regression analysis suggests that PVFS was associated with an increased likelihood of LF/HF ratio. Conclusions: The present study suggests that autonomic dysfunctions are associated with long COVID. Additionally, our findings demonstrate that increased sympathetic activation predicts PVFS.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.24/EE17

Topic: F.06. Autonomic Regulation

Support: NIH Grant R01AA024109

Title: Heart rate variability measures indicating sex differences in autonomic regulation during anxiety-like behavior in rats

Authors: *R. M. FRASIER[1,2], T. DE OLIVEIRA SERGIO[2], P. STARSKI[2], F. W. HOPF[2]; [1]Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [2]Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Mental health conditions remain a substantial and costly challenge to society, especially in women since they have nearly twice the prevalence of anxiety disorders. However, critical mechanisms underlying sex differences remain incompletely understood. Measures of cardiac function, including heart rate (HR) and HR variability (HRV), reflect balance between sympathetic (SNS) and parasympathetic (PNS) branches of the autonomic nervous system. Mounting evidence suggests HRV may be an important transdiagnostic biomarker for and contributor to various pathologies, including those within psychiatry. To better understand sex differences in anxiety-related autonomic mechanisms, we examined HR/HRV telemetry in food-restricted adult rats during novelty suppression of feeding (NSF). NSF presents rats with a conflict between obtaining food and entering the brightly center of the task arena. Previously, our lab showed behavioral sex differences during initial movement and food intake within the NSF. Here, we extend those findings to include HR/HRV patterns that affiliate with such behavioral sex differences. We find at baseline, females had greater HR and lower SNS indicators, as in humans. Also, females (but not males) with higher basal HR carried this state into NSF, delaying first approach to center. In contrast, males with lower SNS indicators had increased approaches and spent more time in the brightly-lit center. Further, females with lower SNS indicators consumed significantly more food during NSF. In males, a subpopulation consumed no food. Among eaters, males with greater SNS indicators consumed more, opposite to females. These data are congruent with human findings suggesting women engage PNS more, and men SNS more, during autonomic regulation. Thus, in females, high basal SNS reduced behavior early in NSF, while subsequent decreases in SNS allowed greater food intake. In males, lower SNS increased engagement with arena center, but greater SNS predicted higher food consumption. Thus, our findings show novel and likely clinically relevant sex differences in HRV-behavior relationships.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.25/EE18

Topic: F.06. Autonomic Regulation

Support: NIH Grant RF1MH125931
NIH Grant R01AG057184

Title: Physiological components of the BOLD signal: relationship with age and heart rate variability biofeedback training

Authors: *R. W. SONG[1], S. WANG[1], J. MIN[2], S. GOODALE[1], K. K. ROGGE-OBANDO[1], C. G. MARTIN[1], M. MATHER[2], C. CHANG[1];
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Abstract: Physiological components of the BOLD signal: relationship with age and effects of heart-rate variability biofeedback training
Song R.W.[1], Wang S. [1], Min J. [2], Goodale S.E.[1], Rogge-Obando K.K.[1], Martin C.G.[1], Yang R. [1], Mather M. [2], Chang C.[1]
[1]Neuroimaging and Brain Dynamics Lab, Vanderbilt University, [2]Emotion and Cognition Lab, University of Southern California
Physiological processes, such as heart rate and breathing, impact the blood oxygen level dependent (BOLD) fMRI signal. While often regarded as noise, BOLD signal fluctuations related to physiological activity may contain valuable information about age-related brain vasculature changes including cerebrovascular arterial stiffening. This study investigates how the dynamics of BOLD responses to physiological activity change with age and in response to heart-rate variability (HRV) biofeedback training, an intervention that affects brain networks implicated in autonomic control. We used the resting-state fMRI and physiological data from the Nathan Kline Institute Rockland Sample Dataset (n = 399). Data were split into younger (<= 36 years) and older (>= 50 years) age groups. Using least squares projection, we fitted physiological impulse functions to model how variation in respiration and heart rate propagate into BOLD signals. We found that percent variance in the BOLD signal explained by physiological signals was significantly higher in younger adults compared to older adults in important regions regulating autonomic responses, including the ventromedial prefrontal cortex, anterior cingulate cortex, insula, and posterior cingulate cortex. In the ventromedial prefrontal cortex, the cross-correlation time lags between BOLD and respiratory signals were also lower in younger compared to older adults. We also examined the Heart Rate Variability (HRV) Biofeedback Training and Emotional Regulation Dataset (n = 193) for a replication analysis. Among older adults, a five-week HRV biofeedback training aimed at increasing heart rate oscillations resulted in higher BOLD-physio covariance in the ventromedial prefrontal cortex, whereas HRV biofeedback aimed to reduce heart rate oscillations yielded no significant effect. These findings highlight the reduced brain-body connection among older adults in brain regions responsible for autonomic activity. They also point to the potential of increasing HRV via biofeedback for improving this connection, potentially improving cerebrovascular health.

Disclosures: R.W. Song: None. **S. Wang:** None. **J. Min:** None. **S. Goodale:** None. **K.K. Rogge-Obando:** None. **C.G. Martin:** None. **M. Mather:** None. **C. Chang:** None.

Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.26/EE19

Topic: F.06. Autonomic Regulation

Support: NSTC Grant 112-2425-H-011-001
NSTC Grant 111-2221-E-182-014

Title: Heart rate variability response to augmented reality exercise programs: exploring the impact of task difficulty

Authors: *P. T. MAI[1], Y.-J. CHANG[1,2], G.-S. LI[1], H.-L. CHAN[1,2], R.-S. CHEN[1,2];
[1]Chang Gung Univ., Taoyuan, Taiwan; [2]Chang Gung Mem. Hospital, Linkou, Taoyuan, Taiwan

Abstract: Augmented reality (AR) exercises provide an engaging and interactive environment that has the potential to affect autonomic balance positively. This study aims to investigate the impact of AR exercise programs on heart rate variability (HRV), examining differences in HRV based on task difficulty levels. The study included 11 healthy adults (6 males and 5 females). The Gentiles model-based exercise protocol that utilizes projected AR comprises a series of tasks divided into four categories: single-task, motor dual-task, cognitive dual-task, and triple-task. These tasks involved walking on both stationary and moving backgrounds. The HRV data was obtained by the Polar H10 sensor chest strap device and analyzed with Kubios HRV software. We used the Pittsburgh Sleeping Quality Index (PSQI) and General Anxiety Disorder-7 (GAD-7) questionnaires to assess sleep quality and anxiety. Participants' perceived difficulty level was assessed using a Likert scale. The results show significant differences between tasks and background conditions. In the motor-dual task, there was higher low-frequency (LF) power ($P < 0.01$) but lower high-frequency (HF) power ($P < 0.05$) when compared to the cognitive-dual task and triple task. Additionally, the motor-dual task had a higher LF/HF ratio than the cognitive-dual task ($P < 0.01$) and triple task ($P < 0.05$). Furthermore, the LF/HF ratio was higher ($p < 0.01$) in the stationary background than in the moving background. The single task exhibited a larger SD1 compared to the triple task ($P < 0.05$). Regarding the Likert self-assessment scale, the Easy level showed a longer RR interval and slower heart rate than the Difficult level. The findings suggest that AR intervention involving cognitive-dual tasks and triple tasks may increase parasympathetic activity, reflected by the changes in HRV parameters. This implies that AR exercise programs can be developed to enhance autonomic regulation and potentially provide HRV benefits.

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Poster

PSTR093. Cardiovascular Regulation

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.27/EE20

Topic: F.06. Autonomic Regulation

Title: Heart rate variability properties in the Mongolian adults

Authors: *E. TUMURBAATAR[1], C. ERDENEBAATAR[1], O. JARGALSAIKHAN[2], A. GANGAA[1], U. ANGARAG[1], T. JADAMBA[3], B. LKHAGVASUREN[4];

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Abstract: Background: Despite the increasing demand for practical ambulatory applications of short-term heart rate variability (HRV), there is a lack of studies investigating the recording of R-R intervals for standard 5-minute analysis of HRV. It has not been extensively validated, and currently, there is no normative data available for the Mongolian general population. The aim of this study was to provide standard 5-minute analysis of HRV by collecting data from a large population consisting of a wide range of age groups. **Methods:** This cross-sectional study was conducted between July 2020 and June 2023. The recording was performed following the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Data were obtained from 1094 participants ranging from 19 to 65 years of age. Age groups were divided as follows: 10-29 years old, 30-39 years old, 40-49 years old, 50-59 years old, and 60-76 years old. In this study, we present the normative data for HRV in these age groups, stratified by gender, as well as for the total participants. **Results:** The data below are expressed as the median with interquartile range (Median (IQR)) in the following order: males (34.8%) and females (65.2%). The time domain indices were as follows: SDNN - 33.84 (20.49) and 32.57 (18.19); RMSSD - 24.32 (20.93) and 24.50 (19.88); NN50 - 12 (44) and 11 (48). The frequency domain indices were as follows: LF power - 176.00 (268) and 153.00 (219); HF power - 96.00 (202) and 104.00 (207); Total power - 536.00 (693) and 509.00 (639); LFnu - 64.35 (26.20) and 58.15 (24.98); HFnu - 35.65 (26.20) and 41.62 (25.05). **Conclusion:** We have provided normative data for HRV in the Mongolian general population.

Disclosures: E. Tumurbaatar: None. **C. Erdenebaatar:** None. **O. Jargalsaikhan:** None. **A. Gangaa:** None. **U. Angarag:** None. **T. Jadamba:** None. **B. Lkhagvasuren:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.01/EE21

Topic: F.07. Biological Rhythms and Sleep

Support: NSF Grant 1736019

Title: The effects of dibutyl phthalate developmental exposure on worker honey bee behavior and circadian rhythms

Authors: *C. RODRIGUEZ ALEMANY, T. GIRAY;
Univ. of Puerto Rico, San Juan, Puerto Rico

Abstract: Honey bees (*Apis mellifera*) are economically and ecologically important plant pollinators that are highly and constantly exposed to environmental stressors including chemical pollutants, which have been linked as one source of honey bee colony losses. Stressor's impact

the bees' complex behaviors, social organization, and division of labor that are regulated by circadian clocks and the rhythms they generate. Honey bees as bioindicators of environmental pollution are an excellent model to study the impact of ubiquitous chemical pollutants such as dibutyl phthalate (DBP) on the circadian rhythmicity ontogeny and plasticity and adult behavioral development of newly emerged workers. Here, the locomotor activity of worker bees, chronically exposed to DBP during their larval or adult stages, was constantly recorded for a period of 15 days to determine the effects of DBP on circadian rhythmicity and behavior. Chronic oral exposure to DBP throughout development affected adult behavioral development, circadian rhythmicity ontogeny, period, rhythm strength, and locomotor activity levels. Our results indicate that environmental DBP stress exposure influences worker honey bee circadian system and behavioral development.

Disclosures: C. Rodriguez Alemany: None. **T. Giray:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.02/EE22

Topic: F.07. Biological Rhythms and Sleep

Title: Spatiotemporal dynamics of cilia length and orientation in the mouse brain

Authors: *R. VAKIL MONFARED[1], S. ABDELKARIM[1], P. DERDEYN[1], K. CHEN[2], H. WU[1], K. LEONG[1], T. CHANG[1], J. LEE[3], S. VERSALES[1], S. NAULI[5], K. BEIER[1], P. BALDI[1], A. ALACHKAR[4];
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Abstract: Primary cilia are hair-like organelles found in most neurons of the mammalian brain. They act as cell antennas, sensing external signals and orchestrating cellular functions. In a previous study, circadian oscillations were observed in cilia genes across different primate brain regions. Building upon this, the current research aimed to investigate the dynamic nature of cilia length and angle and whether they followed a circadian pattern in 22 distinct brain regions. To conduct the study, Swiss Webster mice were perfused every two hours over a 24-hour period, and their brains were collected. Immunohistochemistry was performed using an anti-ADCY3 antibody, specific to cilia. The fluorescent microscope visualized cilia in different regions, and machine learning facilitated the measurement and analysis of cilia length and angle. The findings revealed an average cilia length of 5.15 µm in the whole brain, with variations ranging from 4.79 to 6.33 µm across different regions. The predominant orientations of cilia were towards 180° and 270°, although preferences varied across brain regions. Notably, cilia length exhibited complex daily fluctuations, with distinct patterns during light and dark phases. Several brain regions showed time-dependent changes in cilia length, with some regions displaying maximal lengths during both phases, while others exhibited alternating intervals of peak length. Correlations were

observed in cilia length and angle fluctuations across different brain regions. Strong correlations were found in cilia lengths between the dorsomedial hypothalamus (DMH) and ventromedial hypothalamus (VMH), as well as between the prefrontal cortex (PFC) and several other regions. Conversely, the cilia lengths in the CA1 region displayed negative correlations with the DMH and VMH but positive correlations with other regions such as the retrosplenial cortex (RS), nucleus accumbens (NAc), and dentate gyrus (DG). Cilia length showed circadian Rhythm in NAc core, somatosensory cortex, ARC, DMH and VMH. Similar correlations were identified in cilia angles, with strong correlations in the DMH and VMH and positive correlations among hypothalamic regions and cortices. However, no significant circadian rhythms were observed in cilia angles.In conclusion, this study demonstrates the dynamic nature of cilia length and angle in different brain regions, with complex diurnal fluctuations and correlations. These findings provide insights into the temporal regulation and functional significance of cilia in brain physiology and suggest their involvement in circadian processes and neuronal signaling pathways.

Disclosures: **R. Vakil monfared:** None. **S. Abdelkarim:** None. **P. Derdeyn:** None. **K. Chen:** None. **H. Wu:** None. **K. Leong:** None. **T. Chang:** None. **J. Lee:** None. **S. Versales:** None. **S. Nauli:** None. **K. Beier:** None. **P. Baldi:** None. **A. Alachkar:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.03/EE23

Topic: F.07. Biological Rhythms and Sleep

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Title: Cholecystokinin neurons in mouse SCN are critical for regulating robustness and plasticity of circadian clock

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Abstract: The suprachiasmatic nucleus (SCN) can generate robust circadian behaviors in mammals under different environments. Our recent study using single-cell RNA sequencing has

suggested that SCN neurons can be divided into Avp+/Nms+, Vip+/Nms+, Cck+/C1ql3+, Grp+/Vip+, and Cck+/Bdnf+ subtypes. These neuronal subtypes display distinct circadian gene expression and light responsiveness and occupy different spatial locations in the SCN. Compared with VIP and AVP neurons, cholecystokinin (CCK) neurons showed a delayed phase of circadian clock gene expression. So far, the circadian functions of CCK neurons in the SCN are still unclear. In this study, by monitoring *in vivo* calcium activity and behavioral activities in free-moving animals, we found that the calcium activities of SCN CCK neurons peaked always track the activity onset under different photoperiods, while those of VIP neurons were spread over the entire light phase under a long-day photoperiod. Under LL, the calcium activities of CCK neurons remained oscillating, while those of VIP neurons lost rhythmicity. CCK neurons deficiency led to the shortening of free-running period, and the instability of circadian behaviors specifically under long-day photoperiod and constant light. Furthermore, we found that repeated activation of CCK neurons every 24 hours generated significant phase advances at late subjective night and early subjective day under DD condition, and stably entrain locomotor and temperature rhythms under LL condition. CCK neuron stimulation can only advance the clock but not delay the clock while VIP neuron stimulation can both delay and advance the clock. The impact of VIP neurons on the SCN network was significantly weakened while that of CCK neurons was strengthened in long-day photoperiod. We then found that the response of CCK neuron activity to the sudden change of light-dark cycle is significantly slower than that of VIP neurons and chemogenetic inhibition of CCK neurons can significantly shorten the time of recovery in jet lag. Finally, we simultaneously monitored food consumption (FC), core body temperature (Tb) as well as locomotor activity (LMA) and respectively used optogenetics to activate SCN CCK, VIP and AVP neurons at different five circadian time. We found that SCN CCK and VIP neurons sufficiently regulate FC, Tb and LMA compared with AVP neurons. In summary, we revealed that SCN CCK neurons confer the robustness and plasticity for circadian clock in mouse.

Disclosures: **L. Xie:** None. **Y. Xiong:** None. **D. Ma:** None. **J. Yan:** None.

Poster

PSTR094. Entrainment and Phase Shifts

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Program #/Poster #: PSTR094.04/EE24

Topic: F.07. Biological Rhythms and Sleep

Support: NIH grant F31 EY034387
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NIH grant 1DP2EY022584

Title: Sex-dependent modulation of visual behaviors by the ipRGC molecular clock

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Abstract: Circadian rhythms control many aspects of animal physiology, including modulating sensitivity to sensory stimuli. However, little is known about how peripheral molecular clocks in sensory organs might play a role in this modulation. Here, we investigate whether cell-autonomous clocks in the retina contribute to observed rhythms in visual behaviors in mice. Intrinsically photosensitive retinal ganglion cells (ipRGCs) are a population of retinal cells that contribute to several visual behaviors, some of which are known to be subject to circadian modulation. ipRGCs contain cell-autonomous clocks, and we hypothesize that it is these cellular clocks within ipRGCs that drive the circadian modulation of these behaviors. To test this, we measured various ipRGC-driven behaviors in $Opn4^{cre/+}$; $Bmal1^{fx/fx}$ (Bmal1 cKO) mice, in which the core circadian clock gene Bmal1 is knocked out of ipRGCs exclusively. Our data show that disruption of the ipRGC clock results in deficits in these behaviors, suggesting that the ipRGC clock is necessary for the normal visual function. Additionally, we find that these behavioral deficits are sex dependent.
We then sought to determine how rhythmic gene expression is different in Bmal1 cKO retinas. We used whole retina qPCR to measure retina-wide gene expression in male and female control and Bmal1 cKO mice at four circadian time points. We find that rhythmic gene expression is altered both in the whole retina and in ipRGCs in the Bmal1 cKO mice. Overall, our findings suggest an important and sex-dependent role for the ipRGC molecular clock in retinal function and ipRGC-driven behaviors.

Disclosures: K. Miguel: None. **J. Bhoi:** None. **G. Dyer:** None. **C.P. Ribelayga:** None. **T. Schmidt:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.05/EE25

Topic: F.07. Biological Rhythms and Sleep

Title: Effects of long wavelength red LED lights on circadian rhythm and electroretinogram in C57BL/6 mice

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Abstract: Nocturnal rodents are often housed in rooms with a reverse light cycle so that study procedures may be performed in their active phase in darkness under a red light during normal working hours. We hypothesized that there are long wavelength red light sources which can be perceived by human eyes, but not by rodent eyes due to the lack of red cones, which would eliminate light-induced interference. In this study, we evaluated the effect of different long wavelength red LED lights on circadian rhythm and electroretinogram (ERG) in C57BL/6 mice. Mice were implanted with telemetry devices to collect body temperature and locomotor activity

data. Red (602-662 nm), photo-red (623-688 nm), and far-red (675-777 nm) LED lights, sodium light (569-591 nm), and infra-red LED light (778-878 nm) were tested with white LED light (422-760 nm) as a control. Light intensity was approximately 106 μW/cm^2 (equivalent to white LED at 250 lux) for the circadian study and 0 - 4.23 mW/cm^2 (equivalent to white LED at 0 - 10K lux) in 5 ms light pulses for the ERG study. First, to determine circadian entrainment, animals were placed under a 3-hour delayed 12:12h light:dark cycle. Far-red LED did not cause entrainment, whereas photo-red LED did. Second, to compare their effect on the free-running circadian period vs constant darkness condition, animals were placed under a constant light condition for each test light. Constant far-red LED did not prolong free-running circadian period, whereas constant photo-red or constant sodium light did. Third, to mimic a study procedure, animals were exposed to a 2-hour test light pulse during the dark phase of a standard light cycle. Infra-red LED pulse did not cause noticeable changes in body temperature or locomotor activity profiles, whereas far-red or photo-red LED pulses induced transient changes. Lastly, animals were housed in a room where the dark phase was replaced by a 12-hour test light. Far-red LED in the dark phase did not cause significant change in circadian profiles vs standard light cycle, whereas red LED in the dark phase significantly shortened the alpha (active) period. In the ERG study, the amplitudes of scotopic *b*-wave elicited by infra-red, far-red, photo-red, red, and white LED light pulses at 4.23 mW/cm^2 were 0 ± 0, 37 ± 19, 282 ± 86, 377 ± 109, 521 ± 147 μV (mean ± SD, N = 7), respectively. These results indicate that while far-red LED elicits small photoreceptor responses and induce transient changes in circadian profile, it does not impact the circadian timing system in C57BL/6 mice and may serve as a choice of light source to facilitate studies conducted in the dark phase of a rodent room.

Disclosures: X. Chen: None. **C. Liu:** None. **J. Fenyk-Melody:** None. **S. Kreuser:** None. **D. Hirenallur Shanthappa:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

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Program #/Poster #: PSTR094.06/EE26

Topic: F.07. Biological Rhythms and Sleep

Support: NIMH MH002964
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NIMH IRP MH002952

Title: The paraventricular thalamus conveys aversive information to the central circadian clock

Authors: *M. YURGEL[1], C. GAO[2], M. A. PENZO[2], S. HATTAR[1];
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Abstract: Aversive experiences impact the organization of physiology, metabolism, and behavior around the 24-hr circadian cycle. Studies in rodents have shown that fear-inducing

paradigms can reprogram the central pacemaker, located in the suprachiasmatic nucleus of the hypothalamus (SCN). However, the neural circuits underlying this interaction remain poorly understood. The paraventricular nucleus of the thalamus has recently emerged as a critical node in the regulation of emotional behaviors, such as fear responses. The PVT contains representations of valence and signals arousal state. Among brain regions innervated by the PVT, the SCN receives dense innervations, raising the possibility that PVT-SCN pathways are a key node in mediating the effects of aversive experiences on the circadian system. In this study, we sought to characterize the PVT-SCN circuitry and investigate its functional role. Using retrograde and anterograde tracing methods, we confirmed that the PVT densely innervates the SCN. To further probe the nature of this thalamic-hypothalamic pathway, we performed ex-vivo patch-clamp recordings from SCN neurons while optogenetically stimulating PVT afferents that express channelrhodopsin. We found that the PVT sends monosynaptic glutamatergic inputs to the SCN. Given that the PVT encodes representations of valence, being selectively tuned to aversive stimuli, we wanted to determine if PVT neurons conveyed aversive information to the SCN. We virally targeted GCaMP7s to SCN-projecting PVT neurons and recorded their response to foot shocks using fiber photometry. We found that SCN-projecting PVT neurons are activated by foot shocks. To test if the SCN is sensitive to foot shocks, we used in-vivo fiber photometry-mediated bulk calcium imaging to record from NMS-expressing SCN neurons (SCN^{NMS}). We showed that SCN^{NMS} are activated and inhibited by foot shocks applied at different times of the day. We next investigated whether locomotor activity rhythms were altered in response to aversive stimuli applied at different circadian times (CT). One session of foot shock stress during early- and late-night results in mild phase delays. We next weakened the SCN by applying foot shocks in a constant light environment. We found that locomotor activity rhythms are strongly affected by foot shocks applied at CT14. In agreement, SCN^{NMS} showed an enhanced activation and a reversal of the inhibitory responses to foot shocks applied in a light background. Lastly, we show that chemogenetically silencing PVT neurons reduces the phase delays in response to foot shocks. In summary, we identified a PVT-SCN pathway that seems to relay emotional information to the SCN.

Disclosures: **M. Yurgel:** None. **C. Gao:** None. **M.A. Penzo:** None. **S. Hattar:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.07/EE27

Topic: F.07. Biological Rhythms and Sleep

Title: Food entrainment modifies the content but not the circadian rhythm of neurotransmitter levels in the rat spinal cord.

Authors: *B. JIMÉNEZ ZÁRATE[1], I. JIMENEZ-ESTRADA[2];
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Abstract: FOOD ENTRAINMENT MODIFIES THE CONTENT BUT NOT THE CIRCADIAN RHYTHM OFNEUROTRANSMITTER LEVELS IN THE RAT SPINAL CORD.Jiménez-Zárate B.S. [1,2] ; Jiménez Estrada I. [2].1) Departamento de Fisiología, Biofísica y Neurociencias. CINVESTAV, IPN, MÉXICO.2) Departamento de Fisiología, Escuela Nacional de Ciencias Biológicas, IPN. MÉXICO.In a previous study, we showed that chronic food reduction (50% of control) induces a decrementin the amount and modifies the variability of the circadian content of several neurotransmitters inthe spinal cord of male and female Wistar rats. In such study, we observed that food restrictedrats ingest the food pellets in almost 4 hours (between 8 and 12 hours, day time), so we assumethat timing of meal could influence the content of spinal neurotransmitters. In this study, weexplored the effect of 4-hour day ad libitum food access (FR) on the circadian content variability ofseveral spinal neurotransmitters (glutamate, GABA, dopamine, serotonin, norepinephrine, andepinephrine) and compared it with that of control (CONT) or chronically food deprived male andfemale rats (FD), raised in our institutional animal facility. The content of spinal neurotransmitterswas analyzed by HPLC, in groups of control and experimental male and female rats, randomlysacrificed at 4:00, 8:00, 12:00, 16:00, 20:00 and 24:00 hours, day time. The results obtainedindicate that most of the spinal neurotransmitters analyzed in the FR group (glutamate, GABA,serotonin, adrenaline and dopamine) showed a significant increase in their spinal content but theircircadian variation was similar to that observed in CONT rats. In contrast, food restricted ratsshowed a significant reduction in the content of spinal neurotransmitters and noticeable changesin their circadian variability. It is suggested that the increments in spinal content ofneurotransmitters of the FR group of male and female rats would be associated with a hithertounknown adaptive mechanism, while the changes in neurotransmitters content and circadianvariability of food deprived rats were mainly related to the experimentally induced chronic foodrestriction.

Disclosures: B. Jiménez Zárate: None. **I. Jimenez-Estrada:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.08/EE28

Topic: F.07. Biological Rhythms and Sleep

Title: Circadian entrainment of multiple mice via collective neocortical activity-modulated room light intensity

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Abstract: Humans manipulate electrical devices to optimize the external environment including illuminance, temperature, and humidity. For example, we usually press and release a switch using fingers to turn on and off the room light. Recently, for the remedy for handicapped people,

researchers have developed the brain-machine-interface technique that enables the handicapped to manipulate devices using the information decoded from their neural activity that reflects their internal and external states. Based on the concept of this technique, we hypothesized that the room light can be adjusted directly by information on internal states (i.e., sleep pressure) estimated from neural activity. To test this hypothesis, we chronically implanted electrodes into the prefrontal cortex in a mouse to record slow waves and established a closed-loop experimental system where the light intensity increased when the power of slow waves (i.e., the sleep pressure) became large to evaluate whether the power of the prefrontal slow waves fluctuated in a circadian rhythm.
In physics, when multiple oscillators with different intrinsic frequencies are coupled with each other, the oscillations are synchronized. This phenomenon is called entrainment. However, it remains almost unknown whether neural oscillations of multiple animals are similarly entrained. Given that the circadian rhythm of slow wave powers in a mouse was generated by the interaction between neural activity and the external environment (i.e., light illuminance), we questioned whether slow waves in multiple mice were entrained when common light intensities were determined based on slow waves that were simultaneously detected from these mice. To address this question, we chronically implanted electrodes into the prefrontal cortices. In a training session, we recorded slow waves, obtained a prior distribution of the slow wave power, and associated the distribution with the light intensity. In a test session, we optimized the light intensity every 30 s based on the prior distribution. This experimental system allowed us to observe the circadian entrainment of multiple mice via collective neocortical activity-modulated room light intensity and evaluate the biophysical behavior of coupled ‘neural’ oscillators.

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Poster

PSTR094. Entrainment and Phase Shifts

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Program #/Poster #: PSTR094.09/FF1

Topic: F.07. Biological Rhythms and Sleep

Support: NIHR01 Grant DK078749

Title: Endogenous β -endorphin is required for full expression of the food-entrainable oscillator

Authors: C. CHRISTENSEN[1], C. M. DAIMON[2], *S. T. HENTGES[1];
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Abstract: A food-entrainable oscillator (FEO) is recognized to exist in a variety of mammalian species whereby animals demonstrate anticipatory activity that correlates with scheduled food presentation (food-anticipatory activity; FAA). FAA is a hallmark behavior of animals undergoing activity-based anorexia (ABA), a well-established paradigm in which ad libitum food

access is restricted to specific, limited hours each day and a running wheel is continuously present. The FEO is not reliant upon photo-entrainment or circadian clock genes, and it functions independently of the suprachiasmatic nucleus. However, the anatomical locus, as well as the identity of the cellular and molecular components of the FEO, remain largely elusive. Previous studies have shown that disruption of mu-opioid receptor (MOR) (MOR) signaling substantially reduces FAA during ABA. As β-endorphin is the primary endogenous agonist of MORs, we hypothesized that β-endorphin may play a critical role in FAA. To examine the possibility that the neuropeptide β-endorphin may be a molecular contributor to the FEO and necessary for the expression of FAA, we performed ABA studies utilizing β-endorphin knockout and wild-type (WT) mice of both sexes. Mice were acclimated to single housing and the running wheel for 3 days, then baseline running wheel activity (RWA; automatically collected in 15-minute bins), food intake, and bodyweight data were collected for 5 days of baseline measurement. Mice were then presented chow for only a set 2-h period each day. Time-restricted-feeding was ended when mice reached 80% of their average baseline body weight or after 5 days in the ABA paradigm. During baseline, WT and β-endorphin knockout mice exhibited an equivalent pattern and amount of daily RWA. Once the ABA paradigm was initiated, differences in body weight loss, daily food intake, and the pattern and amount of RWA emerged. β-endorphin knockout mice were slower to reach peak FAA and displayed significantly lower FAA with greater variance compared to WT mice. The β-endorphin knockout mice also remained in the paradigm longer due to having higher daily food intake and slower weight loss. These results show that food entrainment is blunted when β-endorphin is not present, consistent with the work showing the need for functional MORs and elevated β-endorphin during FAA. Altogether, it appears that β-endorphin acting through mu-opioid receptors is needed for rapid and full expression of the FEO. Thus, in addition to its previously described metabolic and feeding-related functions, β-endorphin may also alter food intake and metabolism by modulating food anticipatory responses and the food-entrainable oscillator.

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Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.10/FF2

Topic: B.08. Epilepsy

Support: NIH Grant R01-NS109916

Title: Activity-dependent regulation of core clock genes in neocortical excitatory neurons persists after knockout of Bmal1

Authors: ***E. BARRIOS**[1], M. SHA[5], D. WISE[2], E. KEEFER[3], S. XIAO[1], Y.-H. LIN[1], C. GREGORY[1], M. ROSBASH[6], S. B. NELSON[4];

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Abstract: Recent work from our lab found that the PARbZIP transcription factors and Bmal1 regulate homeostatic plasticity following activity deprivation in excitatory cortical neurons. In order to better understand what genes were impacting homeostatic plasticity, we performed RNAseq following the pharmacological induction or silencing of activity in organotypic slice culture. We found that virtually all other core circadian genes were regulated bidirectionally by activity, which may also implicate them in the regulation of activity-dependent gene expression and homeostatic plasticity. Of note, Clock was found to be increased following activity silencing (log2FC = 0.57, $p<0.001$) and Npas2 was found to be increased following increased activity (log2FC = 1.29, $p<0.001$), which is unexpected since they are known to be compensatory in circadian contexts. In contrast, Bmal1 does not appear to be regulated by activity, and the activity dependent regulation of most of the circadian genes were not impacted by the knockout of Bmal1 in excitatory forebrain neurons, suggesting a non-circadian mechanism of regulation. We also found that the PARbZIPs were robustly increased by activity at a fast timescale, implying they could be part of the primary transcriptional response to activity deprivation. Since the aforementioned genes are known to have robust circadian oscillations in other cell types, we examined their expression over a 24-hour time-course (in equally spaced 4-hour time points) in cortical excitatory neurons via RNAscope of two predominant cyclers (Per2 and Bmal1). This preliminary investigation indicates that there may not be a strong circadian rhythm in the neocortex. Taken together, this work explores a potentially alternative and activity regulated function of known circadian oscillators in the neocortex.

Disclosures: E. Barrios: None. **M. Sha:** None. **D. Wise:** None. **E. Keefer:** None. **S. Xiao:** None. **Y. Lin:** None. **C. Gregory:** None. **M. Rosbash:** None. **S.B. Nelson:** None.

Poster

PSTR094. Entrainment and Phase Shifts

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.11/FF3

Topic: F.07. Biological Rhythms and Sleep

Title: Oscillatory response in cortico-cortical evoked potential examination - response distribution and phase resetting effect on baseline oscillation

Authors: *T. NAKAE[1,2], R. MATSUMOTO[4], K. USAMI[3,5], K. KOBAYASHI[3], M. MATSUHASHI[3], Y. YAMAO[2], T. KIKUCHI[2], T. KUNIEDA[6], A. IKEDA[3], Y. ARAKAWA[2]; [1]Neurosurg., Shiga Gen. Hosp., Moriyama, Japan; [2]Neurosurg., [3]Epilepsy, Movement Disorder and Physiol., Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [4]Neurol., Kobe Univ. Grad. Sch. of Med., Kobe, Japan; [5]Neurol., Yamato Koriyama Hosp., Yamato-Koriyama, Japan; [6]Neurosurg., Ehime Univ. Grad. Sch. of Med., Tou-on, Japan

Abstract: Background. Cortico-cortical evoked potential (CCEP) is a practical method to measure connectivity for the clinical purpose of probing physiological or epilepsy network. Oscillatory response was sometimes observed in the CCEP examination. We investigated where and how often the oscillatory response occurs and performed time-frequency analysis to clarify how the stimulation interacts with the ongoing oscillation.
Methods. Fifteen patients of intractable epilepsy with chronic implantation of subdural electrodes were participated. The seizure onset zone was omitted. Single square pulse (0.3 ms, 4~10 mA) with alternating polarity was delivered through adjacent two electrodes at 1 Hz for routine CCEP of clinical purpose. For the selected stimulus sites which elicited a clear oscillatory response in the same frequency as the background rhythm, the stimulation was performed at a long interval (0.1~0.5 Hz) in another session. The time-frequency analysis was performed on the long interval stimulation data (total 6 sessions; 4 for frontal theta and 2 for parietal alpha). The relationship between pre- and post-stimulus oscillatory parameters (power and phase) was analyzed.
Results. The occurrence rate map revealed that the oscillatory response was distributed in different areas in each frequency band. The distribution pattern was maintained even when the stimulus area was restricted. The time-frequency analysis revealed that the post-stimulus phase distributed around a certain value regardless of the pre-stimulus phase, and that there was no correlation between the pre- and post-stimulus power. The result indicates the oscillatory response is a kind of evoked response, however it is unique in that it lasts longer than the typical CCEP latency, indicating that the stimulation reset the phase of the ongoing oscillation.
Discussion. The oscillatory response was considered to reflect the property of the response site, as the response distribution was constant for different stimulus areas. The fact that an oscillatory response was observed in the frequency of the spontaneous oscillation indicates that the stimulation interacted with the inherent oscillatory nature of the cortex. This study provides fundamental evidence to consider neuromodulation through brain oscillation. As the previous literature reports the effects of transcranial ACS on the working memory performance through the phase locking of the frontal theta, the functional relevance of the phase reset observed in this study is the next concern according to the concept that better understanding of brain function allows more sophisticated mapping, leading to appropriate surgical resection.

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Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR095.01/FF4

Topic: F.07. Biological Rhythms and Sleep

Title: Environmental enrichment unimodally modifies the locomotor activity rhythm in Mongolian gerbils exposed to a short photoperiod

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Abstract: Changes in photoperiod impact animal physiology and behavior. Previous laboratory studies with Mongolian gerbils (*Meriones unguiculatus*) have revealed that short photoperiods of 8h of light and 16h of darkness (LD 08:16) generate negative alterations in the daily rhythm of locomotor activity, as well as depression and anxiety-like behaviors. On the other hand, the implementation of environmental enrichment (EE) in cages proves to be an effective option to reduce stress. In this exploratory study, we asked the following question: Can the effect of short photoperiod on gerbils be attenuated in an enriched environment and, furthermore, can this effect be assessed through the daily rhythm of locomotor activity and the sucrose preference test (SPT)? The objectives were to obtain daily locomotor activity profiles and to evaluate the sucrose preference in order to investigate if they exhibited anhedonic behavior. The gerbils were exposed to LD 12:12 (30 days), to short photoperiod (SD) of LD 8:16 for another 30 days and, finally, they were kept in an enriched environment (SD + EE) for an additional 30 days, which included elements such as an activity wheel, tunnel and shelter within the cage. To individually record locomotor activity, pyroelectric sensors connected to a computer were used and a sampling frequency of 10 minutes was established throughout the experiment. At the end of each phase, the average activity levels of the last 10 days in each condition were analyzed and compared. The SPT was performed after the exposure period in each experimental condition.The obtained results reveal that under a photoperiod of LD 12:12 a bimodal pattern of activity pattern is observed, which becomes fragmented when switching to SD. However, exposure to EE helps to consolidate a more robust unimodal activity profile towards dusk, with only 28% of gerbils maintaining a bimodal pattern. These findings suggest that EE in Mongolian gerbils may strengthen the crepuscular pattern, highlighting the adaptability of these rodents to different photoperiodic conditions. On the other hand, no evidence of anhedonic behavior was found under SD; in fact, we observed that gerbils showed a greater preference for sucrose compared to LD 12:12. This response can be attributed to the gerbils´ ability to adapt to natural conditions, in which they increase their consumption of carbohydrate-rich foods during the short days of autumn and winter to maintain stable body temperature. Conversely, under LD 12:12, gerbils exhibited a very low preference for sucrose, indicating depression-like behavior, possibly due to the negative effects of litter separation.

Disclosures: V. Melo: None. **C. Juarez-Tapia:** None. **M. Miranda-Anaya:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.02/FF5

Topic: F.07. Biological Rhythms and Sleep

Support: NIH NIAAA

Title: Adult and preadolescent methylphenidate leads to changes in sleep/wake activity rhythms in rats

Authors: *L. R. AMODEO[1], C. CUETO[2], A. TEJADA[2], A. CABRERA[3], J. RICHIE[4], M. R. GONZALES[5], S. GOMEZ[2], K. GUERRERO LEON[2];
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Abstract: Children with attention-deficit/hyperactivity disorder (ADHD), whether taking stimulant medications or not, experience more sleep problems than their peers. Since the most common treatment for pediatric ADHD is stimulant medication, there has been a long-standing interest in whether this type of medication results in increased sleep disturbances and the development of sleeping disorders in adulthood. This is of concern since sleep is essential for physical and cognitive development, with sleep problems associated with poorer school performance and a higher likelihood of obesity. One of the most common stimulant medications is methylphenidate (MPH), which has been globally used for over 50 years for the treatment of ADHD in both children and adolescents. This treatment has been shown to improve attention and response inhibition, and reduce hyperactivity in patients with ADHD, as well as in non-clinical human populations and animals. Despite ongoing interest in the association between stimulant use and sleep in children, there is conflicting evidence regarding the impact of MPH on the sleep functioning in children. There is an emerging body of research demonstrating the differential actions MPH can have on a developing system compared to mature adults. Specifically, these studies have found that adult and adolescent MPH treatment can disrupt locomotor diurnal rhythm patterns in rats. The current study investigates the developmental impact of repeated MPH exposure during preadolescent or adulthood on sleep/wake activity quantified using a fitbit-like device on rats. MPH (0 or 2 mg/kg, IP) was administered twice a day for 10 days during either preadolescence or adulthood in male and female long evans rats. Rats were suited with a noninvasive activity monitor (FitBite) in a rodent jacket and activity was recorded in the home cage during baseline, acute MPH exposure (first 24hr), after 10 days of MPH exposure, acute withdrawal, and prolonged withdrawal (10 days after the last exposure day). Data were analyzed using activity count and cosinor analysis. Adult MPH exposure produce circadian rhythm disturbance with shifts in acrophase and amplitude. Additionally, increases in fragmentation of rest-activity during the light period occurred after prolonged withdrawal.

Disclosures: L.R. Amodeo: None. **C. Cueto:** None. **A. Tejada:** None. **A. Cabrera:** None. **J. Richie:** None. **M.R. Gonzales:** None. **S. Gomez:** None. **K. Guerrero Leon:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.03/FF6

Topic: F.07. Biological Rhythms and Sleep

Support: NICHD; P50 HD103573
UNC SURF award to DR

Title: Methods for sleep disruption in mice: stimulant-induced versus a nonpharmacological approach

Authors: *K. HARPER, D. REICH, M. CONRAD, S. MOY;
UNC Chapel Hill, Chapel Hill, NC

Abstract: Methods for sleep disruption in mice: stimulant-induced versus a nonpharmacological approach
Kathryn M Harper, Ph.D.[1-2*], Daniel Reich[1-2], Monika E. Conrad[1-2], and Sheryl S. Moy, Ph.D.[1-2]
Department of Psychiatry[1], Carolina Institute for Developmental Disabilities[2], University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC. USA.
Understanding the best method to induce sleep disruption (SD) could prove useful for determining methodologies for testing for sleep disorders in mice, as a significant number of neurological/neuropsychiatric disorders are associated with irregular sleep. In the case of mouse models that do not exhibit abnormal sleep patterns under typical conditions, utilizing a SD challenge, via stimulants or otherwise, could reveal an underlying vulnerability to sleep loss or impaired sleep recovery. In this study, C57BL/6J male and female mice, at eight weeks in age, were evaluated in a piezoelectric sleep system for eight days on a 12/12 hr light/dark cycle. On the sixth day, during the light-phase, mice either underwent a 3-hour nonpharmacological SD or pharmacological SD (either 3.0 mg/kg amphetamine, 12.5 mg/kg caffeine, or saline, administered i.p.). Nonpharmacological SD (also known as novelty-induced disruption) consisted of introducing the mice to a series of novel behavioral testing chambers and cage conditions. The results showed that the novelty-induced sleep disruption caused an increase in percent sleep in the early hours of the dark phase following SD in both sexes, while the stimulant-treated groups showed small or no differences in percent sleep. These findings indicate that novelty-induced disruption was more likely than stimulant drugs to cause rebound effects later in the sleep cycle. Additionally, female mice were shown to sleep less under baseline conditions and have less significant sleep rebound than male mice. The impact of novelty-induced SD was confirmed in a separate set of C57BL/6J male and female mice, evaluated for sleep patterns four weeks after undergoing a standard phenotyping regimen. Overall, the results suggest that novelty-induced SD could be a useful addition to studies on sleep patterns and response to sleep deprivation in mice.

Disclosures: K. Harper: None. **D. Reich:** None. **M. Conrad:** None. **S. Moy:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.04/FF7

Topic: F.07. Biological Rhythms and Sleep

Support: Wendy and Leonard Goldberg endowment to UCLA

Title: Continuous long-term recording of brain neurovascular activity and behavior in freely moving mice reveal effects of chronic caffeine on circadian patterns of brain blood flow and sleep

Authors: K. AFRAMIAN[1], D. YOUSEF YENGEJ[2], S. NWAOBI[3], A. C. CHARLES[4], ***G. FAAS**[2];
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Abstract: We recently developed an inexpensive, minimally invasive microchip system to continuously monitor (over weeks) cerebral blood volume, heart rate, heart rate variability, head movement, sleep stages and multiple other physiological and behavioral parameters in freely behaving mice. Behavior is also monitored with simultaneous video recording. The same system can be used for transcranial optical triggering of cortical activity in mice expressing channelrhodopsin. To test the utility of this system we studied the effects of caffeine on some of the mentioned parameters in mice.
Caffeine has complex effects on neurovascular activity and behavior throughout the circadian cycle. How chronic use of caffeine has long lasting/chronic effects on sleep and behavior is not completely clear.
We used our system to continuously record effects of chronic caffeine in the drinking water of freely behaving mice. Caffeine shifted both sleep and awake phases by up to 2 hours relative to the light-dark cycle. During caffeine administration, rapid eye movement (REM) sleep was inhibited during the awake phase and shifted to a greater extent than nonREM sleep during the sleep phase. Caffeine also altered circadian patterns of cerebral blood volume, causing progressively *decreased* mean CBV throughout the awake phase and progressively *increased* mean cerebral blood volume throughout the sleep phase, despite less awakening and less movement during the sleep phase. Chronic caffeine increased average heart rate during sleep but not during the awake state, and increased heart rate variability in both states. These results provide new insight into the effects of caffeine on circadian biology.
With its capacity to continuously and synchronously record multiple types of physiological and behavioral data over extended time periods our inexpensive method has the potential for widespread practical application in rodent research.

Disclosures: K. Aframian: None. **D. Yousef Yengej:** A. Employment/Salary (full or part-time):; UCLA. 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.; Goldberg Migraine Program. **S. Nwaobi:** None. **A.C. Charles:** A. Employment/Salary (full or part-time):; UCLA. 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.; Wendy and Leonard Goldberg endowment, Meyer and Renee Luskin Chair in Migraine and Headache Studies. **G. Faas:** A. Employment/Salary (full or part-time):; UCLA. 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.; Goldberg Migraine Program.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.05/FF8

Topic: F.07. Biological Rhythms and Sleep

Support: Wellcome Trust 215267/Z/19/Z

Title: Boosting sleep improves motor learning in mice

Authors: *R. SIMAYI[1], S. GALIZIA[3], R. AVVISATI[4], L. DE VIVO[1], M. BELLESI[2,4];
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Abstract: Growing evidence has shown that it is possible to enhance sleep time and intensity in a drug free and non-invasively manner by delivering sensory stimulation during sleep. Different sensory modalities such as auditory and vestibular stimulations have been proven effective in boosting sleep. However, the cognitive and cellular consequences of sleep enhancement with sensory stimuli remain still unclear. In the current study, we investigated the effects of sleep enhancement on motor learning and cortical gene expression in young adult mice.We took advantage of a recent discovery showing that NREM sleep can be extended in mice by gently rocking them with an orbital shaker. Thus, C57BL/6 male mice (post-natal day 45) were divided in normal sleep (S, n=12) and sleep enhancement (SE, n=15) groups. S mice were left undisturbed, while SE mice were rocked at 1 Hz for 12h/day during the light period for 11 consecutive days. During this period, all mice had access to a complex wheel for 12h/day during the dark period. Food and water were available ad libitum. Mouse motion activity was continuously detected with infrared camera and used as a proxy of sleep and wake behavior. Motor learning was calculated as ratio between final (day 11) and initial (day 1) maximum and average speed. Finally, mice were sacrificed, and mouse motor cortex was quickly dissected and processed for standard RNA sequencing. We found that SE mice slept overall longer than S mice, with a daily increase in sleep time ranging from 2.05% to 9.04% ($p=0.02$). SE also showed an average lower number of sleep to wake transitions indicative of more consolidated sleep ($p<0.001$). SE group showed improved learning relative to S group ($p=0.042$ for average speed, $p=0.016$ for maximum speed) and the extent of learning was correlated with the amount of sleep in both S and SE mice ($r=0.598$ $p=0.001$ for average speed; $r=0.596$ $p=0.001$ for maximum speed). Moreover, gene expression analysis (with a threshold of 0.05 on the adjusted p-value and an absolute log2 fold change of 0.38) revealed 139 genes that were differentially expressed between S and SE. Of those, 73 genes were upregulated, and 66 genes were downregulated by SE. A subsequent functional enrichment analysis revealed that top significant classes of genes were involved in the regulation of glutamatergic synapses and synaptic plasticity. Thus, sleep enhancement via rocking increases sleep duration and promote motor learning performance in mice. This effect is associated with changes in the expression of genes implicated in synaptic transmission.

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Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.06/FF9

Topic: F.07. Biological Rhythms and Sleep

Support: NIH RO1AG072513

Title: Continuous Video Actigraphy for Longitudinal Murine Sleep Architecture and Exercise Monitoring

Authors: *C. J. BOUCHER[1,2,3], K. K. NAYLOR[2,3], T. M. SHERRY[2,3], E. A. PROCTOR[2,3,5,6], P. J. DREW[1,2,3,4,5], B. J. GLUCKMAN[1,2,3,4,5];
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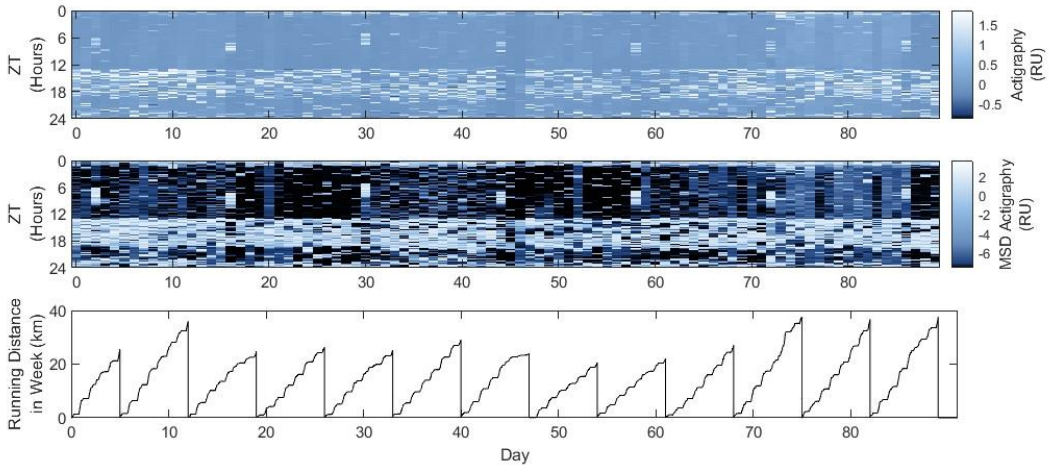
Abstract: Over the course of normal aging, and in neurological disease, sleep patterns and baseline sleep architecture shift. Disruptions to normal sleep patterns and sleep architecture have been linked to the development of a variety of neurological diseases. These changes in baseline sleep architecture and sleep regularity occur over natural aging as well. In the brain, sleep acts as a vasodilator, where changes in the vascular network and extracellular space fraction serve as a potential mechanism for metabolic waste clearance. Exercise is thought to modulate sleep architecture in a way that improves sleep quality and is correlated to ameliorating symptoms associated with neurological disease. However, it is unknown how and when the bidirectional interaction between sleep and exercise affects either normal aging or aging in neurological disease. Here we have implemented a robust, noninvasive system for continuous, long-term recording of behavior and activity in mice. These recordings will allow us to quantify several measures that can be used to compare different cohorts of animals: animals with unlocked running wheels (Free wheel, FW) and those with locked running wheels (Locked Wheel, LW). Activity measures are obtained using a video-based actigraphy tracking software housed within the cage system. Motion is detected and quantified from changes in the pixel intensity across consecutive frames in real time. Using actigraphy tracking methods, we can differentiate between low impact activity (I.e., grooming, sleeping, resting) and high impact activity (I.e., running). Additional measures we extract include wheel rotation counts and animal location within the cage, and time spent running. Further work will be done to distinguish between sleep states and measure sleep consolidation.



Disclosures: **C.J. Boucher:** None. **K.K. Naylor:** None. **T.M. Sherry:** None. **E.A. Proctor:** None. **P.J. Drew:** None. **B.J. Gluckman:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

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Program #/Poster #: PSTR095.07/FF10

Topic: F.07. Biological Rhythms and Sleep

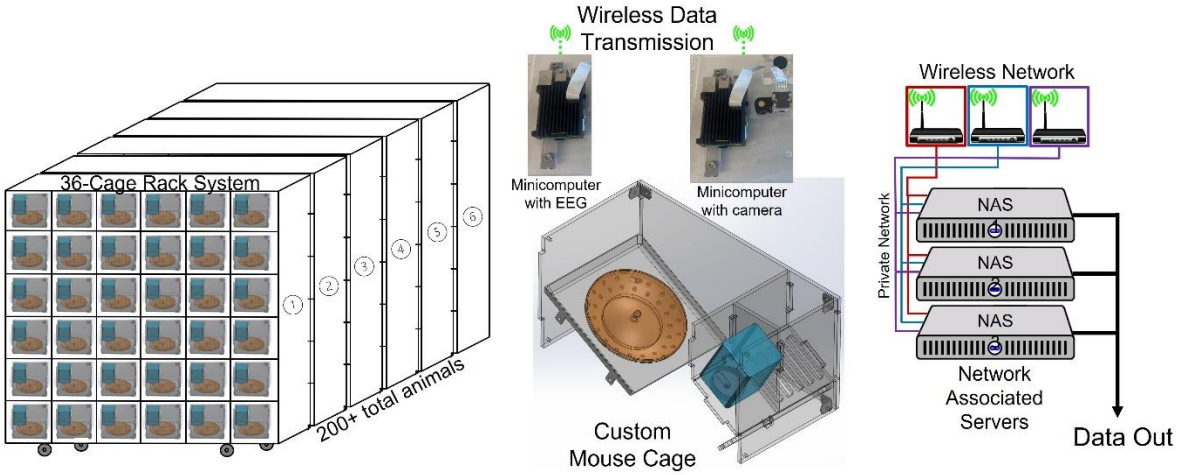
Support: NIH R01AG072513
NIH T32NS115667

Title: Longitudinal Murine Sleep Architecture and Exercise Monitoring

Authors: *K. K. NAYLOR[1,2,3], C. J. BOUCHER[1,2], T. SHERRY[1,2], E. A. PROCTOR[1,2,4,5], P. J. DREW[1,2,4,6], B. J. GLUCKMAN[1,2,4,6];
[1]Engin. Sci. and Mechanics, [2]Ctr. for Neural Engin., [3]Cross Disciplinary Neural Engin., [4]Neurosurg., [5]Pharmacol., [6]Biomed. Engin., Pennsylvania State Univ., University Park, PA

Abstract: Sleep patterns naturally evolve over the lifespan of an animal, but sleep disorders commonly develop as secondary factors underlying a variety of neurological diseases. Disruption of sleep - regardless of cause - has been identified as a risk factor for neurological diseases and is potentially implicated in the mechanisms underlying disease progression. Prospective observational studies have shown that physical inactivity is one of the most common preventable risk factors for neurological disease. It is commonly accepted that exercise has positive benefit on sleep-wake regulation, but less is known about how other factors (i.e., sex, age, sleep quality, activity) mediate this complex system. Sleep and exercise interact through a series of complex, bidirectionally linked processes that affect multiple downstream physiologic pathways. We can probe the interactions between sleep and exercise in freely behaving animals using a custom

designed cage and acquisition system. Our goal was to design a robust system that allows for continuous, long-term observation of large colonies of mice over the course of normal aging and in models of neurodegenerative disease. Activity and exercise are monitored at low resolution using video-based actigraphy tracking while high resolution state of vigilance (SOV) and neural activity can be recorded via intracranial electroencephalogram (iEEG). Additional health information (i.e., relative humidity, cranial temperature, cage temperature) can be monitored, and the system is designed to allow for additional instrumentation. Using this system, we can quantify baseline measures sleep architecture and general exercise, as well as how those measures shift over the course of aging. The system has been live since January 2023, and currently records robustly and continuously from a cohort of fifty animals. Our goal in the upcoming months is to continue testing and ramping up the system until it can continuously and reliably record from a cohort of two hundred animals.



Disclosures: K.K. Naylor: None. **C.J. Boucher:** None. **T. Sherry:** None. **E.A. Proctor:** None. **P.J. Drew:** None. **B.J. Gluckman:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.08/FF11

Topic: F.07. Biological Rhythms and Sleep

Support: P50 MH103222

Title: Maternal kynurenine 3-monooxygenase genotype in mice directs sex-specific behavioral outcomes in offspring

Authors: *M. V. PIROLI[1], S. MILOSAVLJEVIC[1], E. J. SANDAGO[1], G. G. PIROLI[1], N. FRIZZELL[1], S. BEGGIATO[2], A. POCIVAVSEK[1];

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Abstract: Both genetic and environmental influences impact outcomes of neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD), schizophrenia (SZ), and bipolar disorder (BD). Cognitive impairments, sleep disturbances, and anxiety are highly prevalent comorbidities in these patients. Kynurenine 3-monooxygenase (KMO) is a pivotal branch-point in the kynurenine pathway (KP) of tryptophan metabolism. Reduced *Kmo* mRNA expression and KMO enzyme activity are found in postmortem brains of individuals with SZ. To further characterize the relationship between NDD endophenotypes and alterations in *Kmo*, we presently used mice with heterozygous (HET-*Kmo*$^{+/-}$) parental origin to generate wild-type offspring (WT-*Kmo*$^{+/+}$), while offspring from C57BL/6J wild-type parental origin were the control (WT-Control) group. Adult offspring were used for behavioral testing, either in Barnes maze (BM) or in elevated zero maze (EZM), or sleep experiments, by implanting telemetry transmitters to continuously monitor electroencephalogram (EEG) and electromyogram (EMG) in freely moving mice. Sleep-wake behavior was also evaluated in HET-*Kmo*$^{+/-}$ mice. KP metabolites in breast milk and mitochondrial respiration in brain regions were analyzed in HET-*Kmo*$^{+/-}$ and WT-Control females, the parental genotypes. Female WT-*Kmo*$^{+/+}$ offspring were impaired in BM spatial learning traveling a significantly longer distance ($P<0.01$) and committing a higher number of errors ($P<0.05$) concurrently with increased immobility in the maze ($P<0.05$). WT-*Kmo*$^{+/+}$ females exhibited increased anxiety-like behavior in EZM with fewer entries to the open area ($P<0.05$). Sleep duration was decreased in female WT-*Kmo*$^{+/+}$ mice along with significantly prolonged wakefulness ($P<0.05$). Male WT-*Kmo*$^{+/+}$ offspring were impaired in BM reversal learning when compared to their counterpart controls ($P<0.05$). Both female and male HET-*Kmo*$^{+/-}$ mice displayed reduced sleep duration ($P<0.01$) and altered EEG power spectra (genotype x frequency: $P<0.0001$) relative to WT-Control mice. Breast milk kynurenine was significantly higher in HET-*Kmo*$^{+/-}$ than in WT-Control mothers ($P<0.0001$). Adenosine diphosphate (ADP)-linked maximal respiration (State 3) was decreased in cortical mitochondria in HET-*Kmo*$^{+/-}$ vs. WT-Control female mice, with a significant decrease in the respiratory control ratio ($P<0.001$). Taken together, our results suggest that maternal *Kmo* genotype imposes adverse behavioral outcomes in offspring in parallel with region specific alterations in brain mitochondrial metabolism.

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Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.09/FF12

Topic: F.07. Biological Rhythms and Sleep

Support: the Alfred P. Sloan Foundation (A.E.-R.)
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the Brain and Behavior Research Foundation Young Investigator Grant (A.E.-R. and G.R.)
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Sleep Research Society Small Grant (M.I.S.)
Sigma-Xi Grant in Aid of Research (C.K.)

Title: Seeking contact and synchrony: deciphering the impact of social interactions on sleep patterns and physiology in mice

Authors: *M. I. SOTELO[1], C. KOHTZ[2], T. KUDLAK[2], C. MARKUNAS[2], A. L. VYSSOTSKI[3], G. ROTHSCHILD[2], A. EBAN-ROTHSCHILD[2];
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Abstract: Social interactions are an important component of animal life, profoundly influencing development, physiology & behavior. Yet, how sleep-a central behavioral & neurophysiological process-is modulated by social interactions is poorly understood. In this study, we characterized sleep behavior & physiology in freely moving and co-living mice under different social conditions. We utilized wireless neurophysiological devices to record simultaneously from multiple individuals within a group for 24 hours, along with video acquisition. We first characterized pre-sleep behavior & demonstrated that mice seek physical contact before sleep initiation & sleep while in close proximity to each other (hereafter, 'huddling'). To determine whether huddling during sleep is a motivated behavior, we devised a novel behavioral paradigm which allows mice to choose whether to sleep in close proximity to a conspecific or in solitude, under different environmental conditions. We also developed a machine learning-based approach to automatically classify huddling behavior. We demonstrate that mice are willing to forgo their preferred sleep location, even under thermoneutral conditions, to gain access to social contact during sleep, strongly suggesting that the motivation for physical contact during sleep drives huddling behavior. We then characterized sleep architecture under different social conditions & uncovered a social-dependent modulation of sleep. We also revealed coordination in multiple neurophysiological features among co-sleeping individuals, including the timing of falling asleep & waking up & NREM sleep intensity. Notably, the timing of REM sleep was synchronized among co-sleeping male siblings but not co-sleeping females or unfamiliar mice. Our findings provide novel insights into the motivation for physical contact during sleep and the extent of social-dependent plasticity in sleep, offering a framework for further explorations into the neuronal mechanisms underlying these processes. A better understanding of the intersection between social living & sleep could also advance current understanding of the functions & evolution of sleep.

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Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.10/FF13

Topic: F.07. Biological Rhythms and Sleep

Support: Grass Foundation
Kavli Foundation
Marine Biological Laboratory, Woods Hole, MA, U.S.A.
Centre of Neural Computation 223262
Centre for Algorithms in the Cortex 332640
Ministry of Science and Education, Norway

Title: Modulation of active sleep following salient social encounters in the cuttlefish Sepia Bandensis

Authors: *N. WANIEK[1], B. DUNN[2], H. A. OBENHAUS[1];
[1]Kavli Inst. for Systems Neurosci., Trondheim, Norway; [2]Dept. of Mathematics, Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: Sleep and the interplay between sleep and memory are among the most intensely studied phenomena in modern neuroscience (Maquet, 2001). Discoveries in the brains of rodents and birds promoted the hypothesis that ordered reactivation (*replay*) of recent experiences during sleep aids the formation of stable memory traces (Wilson and McNaughton, 1994; Dave and Margoliash, 2000). Yet, the physiological significance of replay remains enigmatic. Coleoid cephalopods (octopuses, cuttlefish, and squid) possess a rich behavioral repertoire and can acquire complex memories. Recently, members of these species were reported to show signs of REM-like, “active” sleep. In cuttlefish, this is accompanied by overt and fast changing chromatophore activity (Frank et al., 2012; Iglesias et al., 2019). Here we leverage the uniqueness of the chromatophore system, which is directly innervated by the central cephalopod brain, to non-invasively study neural activity via skin patterning.
The stumpy-spined cuttlefish, *Sepia Bandensis*, tolerates rearing in groups and exhibits a variety of distinct skin patterns. We noticed that while cuttlefish interact, they display dynamic and colorful chromatophore activity. We hypothesize that skin pattern dynamics during active sleep show signs of reactivations of prior social encounters, akin to replay in the brain of vertebrates. Here we show data from continuous video recordings of eight *S. Bandensis* over several weeks. During this time, we exposed individuals to each other, repeating all possible pairwise combinations at least once. We ran trials in a novel behavioral arena that allows for exposure and isolation of cuttlefish without invasive manipulation of the behavioral space. All animals fell asleep regularly during both day and night, and frequently exhibited active sleep periods. During social interactions, *S. Bandensis* females and males displayed previously undescribed, rapidly changing skin patterns, which varied in content and dynamics from baseline camouflage activity. Using custom image analysis routines we extracted a library of cuttlefish mantle and head region patterns from both baseline (isolated individuals) and social interaction trials. With the resulting pattern space we are able to compare patterns occurring during active behavior and sleep. We are currently exploring how skin displays in *S. Bandensis* are used for social communication and if

active sleep periods that follow social interactions differ in frequency, duration or pattern content from baseline trials. This will yield preliminary evidence of whether and how replay phenomena in cephalopod nervous systems relate to those studied in vertebrates.

Disclosures: **N. Waniek:** None. **B. Dunn:** None. **H.A. Obenhaus:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR095.11/FF14

Topic: F.07. Biological Rhythms and Sleep

Support: Grass Foundation
Kavli Foundation
Marine Biological Laboratory, Woods Hole, MA, U.S.A.
Centre of Neural Computation 223262
Centre for Algorithms in the Cortex 332640
Ministry of Science and Education, Norway

Title: Development of quiet and active sleep states in Octopus Bimaculoides juveniles

Authors: *H. A. OBENHAUS;
Kavli Inst. For Systems Neurosci., Trondheim, Norway

Abstract: Sleep is an essential component of our lives and, as a systems-level process, it is remarkably conserved across animal phyla (Campbell and Tobler, 1984; Jha and Jha, 2020). Electrophysiological recordings in the brains of vertebrates have led to the discovery of two distinct sleep stages, slow wave (SW) and rapid eye movement (REM) sleep (Diekelmann and Born, 2010). However, the development and physiological relevance of these two sleep stages are still unknown. Mounting evidence suggests that distinct sleep states may also exist in reptiles (Shein-Idelson et al., 2016) and recently, cyclic alternations between REM-like sleep or “active” sleep and quiet sleep states have been described in coleoid cephalopods, which possess highly evolved nervous systems that support behavioral flexibility on par with that of small mammals (Frank et al., 2012; Mather and Dickel, 2017; Iglesias et al., 2019). In cuttlefish and octopuses, active sleep is accompanied by bouts of rapidly changing chromatophore activity (skin patterning). Since small groups of chromatophores are directly innervated by the central cephalopod brain, this discovery enables the non-invasive study of nervous system activity in these species. Here we obtained continuous video data from more than 20 *Octopus bimaculoides* at different developmental time points (1-5 months post-hatching). Individual octopuses were filmed for weeks during both day and night in behavioral arenas that allowed for simultaneous monitoring of three orthogonal views on the same animal. Automated tracking algorithms enabled the coarse quantification of skin pattern changes as well as locomotor activity throughout the day and night. Vibratory stimuli presented at varying strength and at random

intervals allowed for discrimination of quiescence versus sleep in all animals. Using these data we observed, for the first time in *O. bimaculoides*, active and quiet sleep states that occurred during both day and night. By following different age groups over days and weeks we were able to study the development of ultradian sleep/wake rhythms and sleep stages in juvenile octopuses, which is difficult to achieve in other model organisms. Preliminary results suggest that active sleep states can be observed as early as 6 weeks after hatching. The fast development, complex nervous system as well as the uniqueness of the central neuronal innervation of the chromatophore system make *O. bimaculoides* an attractive model system for studying sleep development, which opens the door to comparative systems analyses across largely distinct, yet similarly complex brain architectures.

Disclosures: H.A. Obenhaus: None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.12/FF15

Topic: F.07. Biological Rhythms and Sleep

Support: Facultad de Medicina, UNAM

Title: Destabilizing sleep and hierarchies in crayfish.

Authors: S. JÁUREGUI-DURÁN[1], N. CAMACHO-LÓPEZ[1], A. DE LA O-MARTÍNEZ[2], K. MENDOZA-ANGELES[3], ***J. G. HERNANDEZ-FALCON**[4];
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Abstract: Hormonal activity regulates metabolism and is a fundamental piece in homeostatic control. In invertebrates as well as in vertebrates stress conditions induce the interplay of different hormones that regulate energetic expenditure and preserve life or integrity of the organism. In decapod crustaceans the main hormone involved in stress response is the Crustacean Hiperglycemic Hormone (CHH, part of a superfamily involved in multiple homeostatic regulations). This compound keeps glucose levels elevated during stress conditions, is synthesized in the X-organ and stored in the sinus gland, both allocated in the eyestalk (lateral protocerebrum). Agonistic interactions are stressful situations that terminate in the formation of a hierarchy with a dominant animal and one o more subordinates. The establishment of this hierarchy can be perturbated by the lack of sleep, a condition in which animals prefer sleep to fight. We investigated if the reduction of hormones released by the sinus gland modifies the sleeping pattern or the hierarchy formation in triads of adult crayfish *Procambarus clarkii*. Surgical resection of both sinus glands resulted in a decrease in number and duration of sleeping bouts and total sleeping time. In animals without sinus glands the hierarchical order was not

stable and dominance oscillated among contenders. These results imply hormonal regulation in both processes, the mechanisms could be related to energetic use-storage. Supported by Facultad de Medicina, UNAM.

Disclosures: **S. Jáuregui-Durán:** None. **N. Camacho-López:** None. **A. De la O-Martínez:** None. **K. Mendoza-Angeles:** None. **J.G. Hernandez-Falcon:** None.

Poster

PSTR095. Sleep: Behavioral Studies in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.13/FF16

Topic: F.07. Biological Rhythms and Sleep

Support: UNAM-PAPIIT IN228523

Title: Sleep deprivation induces alteration in memory consolidation in crayfish

Authors: R. AGUAYO-SOLÍS, M. OSORIO-PALACIOS, J. HERNÁNDEZ-FALCÓN, *K. MENDOZA-ANGELES;
Univ. Nacional Autonoma de Mexico, México, Mexico

Abstract: Sleep (or at least a physiological period of quiescence) is widely distributed among animals, ranging from fruit flies to humans, but despite our major understanding into its mechanisms over the last 50 years, the biological function of sleep remains a mystery. Furthermore, we know that complete sleep deprivation induces death in experimental animals. We have previously demonstrated that the crayfish, Procambarus clarkii, fulfills the behavioral and electrophysiological criteria of sleep. Besides, when placed in social interaction, decapods display an agonistic behavior that results in the establishment of a hierarchical structure. In triads of crayfish, repeated social interactions form a recognition memory. In this study, we aim to determine the relationship between sleep deprivation and the formation of this recognition memory in P. clarkii. We recorded five days of agonistic encounters in control (n=6) and sleep deprived triads (in which we performed 1 hour of sleep deprivation immediately after the agonistic interaction, n=6). As previously reported, in the control triads the intensity of the encounters de-escalated steadily on the 5 days of interaction and also the dynamic of the interactions changed as individuals recognized each other, with an increase in proportion of threats and avoidances, while attacks and fights decreased. Moreover, in the sleep deprived triads, we do not observe a decrease in the intensity of the agonistic interaction, nor a change in the dynamic of the encounter. These results indicate that sleep deprivation impairs the normal establishment of the recognition memory in crayfish. Although we do not know the mechanism by which sleep deprivation inhibits the formation of this memory in crayfish, these findings support the hypothesis that sleep is a fundamental brain process whose origins go back early in the phylogeny.

Disclosures: **R. Aguayo-Solís:** None. **M. Osorio-Palacios:** None. **J. Hernández-Falcón:** None. **K. Mendoza-Angeles:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.01/FF17

Topic: G.03. Motivation

Support: HHMI
Simons Collaboration on the Global Brain
NIH

Title: Uncovering the neural logic of mate selection in Drosophila

Authors: ***R. LI**, T. HINDMARSH STEN, V. RUTA;
Rockefeller Univ., New York, NY

Abstract: Males of many species have evolved behavioral traits to attract mates and compete with rivals. Here, we explore mate selection in *Drosophila melanogaster* from both the male and female perspective to shed light on how the key components of sexual selection-female choice and male-male competition- work in concert to guide reproductive strategies. Male flies perform an elaborate courtship ritual to entice a female to mate, including pursuing her and vibrating a single wing to produce a species-specific courtship song. In the wild, however, these courtship rituals unfold amidst a much more complex social landscape. *Drosophila* congregate and mate on their host plants, creating a competitive environment where females are often pursued by multiple males concurrently. To understand how females select between competing conspecific mates, we paired a female with two males and assessed male courtship strategies. Through pose-tracking and quantitative behavioral analysis, we demonstrate that competing males rapidly alternate between courtship and agonistic behaviors, characterized by distinct bilateral wing flicks. We demonstrate that these agonistic wing flicks produce acoustic signals that jam the auditory pathways of the female, impeding her detection of advertising signals from other males. Consequently, females rarely accept a mate when she is actively pursued by both males. Moreover, agonistic wing flicks serve to physically repel a male's rivals, enabling him to overcome the acoustic interference from his competitors and gain sole access to the female. Reproductive success, therefore, requires that males persistently court females while also executing agonistic wing flicks to drive competitors away. Combining optogenetic perturbations and functional imaging in tethered males interacting with virtual fly targets, we elucidate the circuit architecture mediating the rapid alternation between courtship and agonistic behaviors based on sex-specific sensory signals. By examining both behavioral and neural dynamics during competitive courtship in both males and females, we describe the neural logic underlying the mate selection process in *Drosophila* and gain insights into how female preferences and male-male competition guide mate choice.

Disclosures: **R. Li:** None. **T. Hindmarsh Sten:** None. **V. Ruta:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.02/FF18

Topic: G.03. Motivation

Support: NIH Grant P20GM125508
Hawaii Community Foundation 18CON-90818

Title: Metabolic ketosis shifted the gene expression landscape to promote social affinity in a genetically asocial fish population

Authors: *M. YOSHIZAWA[1], A. TRAN[1], J. CASHON[1], M. GARCIA[1], R. BALMILERO-UNCIANO[1], V. SALGADO[1], D. BURBANO[1], M. WONG[2,4], R. LEE[5,3], M. IWASHITA[1]; [1]Sch. Life Sci., Univ. of Hawaii, Honolulu, HI; [2]Nutr. Services Dept., [3]Med. Staff Dept., Shriners Hosp. for Children, Honolulu, HI; [4]Nā Pu‘uwai Native Hawaiian Healthcare Syst., Honolulu, HI; [5]Dept. of Pediatrics, Univ. of Hawaii at Manoa, Honolulu, HI

Abstract: Social affinity, the tendency for two or more individuals of the same species to form close associations, is nearly ubiquitous in the animal kingdom, but many species independently lost it according to their ecological demands during evolution. However, social affinity is still fundamental in asocial species such as mating; and it is unclear which molecular factors in the brain turn on the switch for the hidden social affinity in these asocial species. Recent studies hinted that the ketosis-inducing ketogenic diet treatment improved the sociality score of Autism Diagnostic Observation Schedule-2 (ADOS-2) in patients with autism. The ketogenic diet induces a state of ketosis in the whole body, and the cells and neurons preferentially use ketone bodies instead of glucose as a primary energy source. The molecular and genetic mechanisms for how ketone bodies promote social affinity are largely unknown. Previous comparative gene expression studies in the asocial Mexican cavefish revealed that the dysregulated genes in this population are significantly enriched in homologs of autism risk-associated genes (SFARI genes), and its social affinity was recuperated by the ketogenic diet, fasting, or administration of exogenous ketones. We then hypothesized that ketone bodies promote social affinity by adjusting many dysregulated autism-risk genes. Here we used the Mexican tetra fish *Astyanax mexicanus* as an experimental model. *A. mexicanus* exists in two morphological forms: asocial cave-dwelling (cavefish) and social riverine (surface fish) forms. Cavefish were derived from the surface fish-type ancestor and adapted to the food-sparse dark environments. In this environment, they display asociality and exhibit 58.5% of the same directional gene expression changes (up- or down-regulations) out of ~4,000 dysregulated genes seen in patients with autism. The 58.5% overlap exceeds mammalian platforms (~10%). In contrast, surface fish show typical social behaviors. During the ketogenic diet treatment, we also observed a wide variation of responding and non-responding cavefish to this treatment, possibly due to their naturalistic

heterogeneity. We developed a new method to disentangle the relationship between the genes and ketosis in the context of social affinity by developing a method for detecting correlations in high dimensional data between the serum metabolites, brain transcriptome, and social affinity, and we will present it in this meeting.

Disclosures: **M. Yoshizawa:** None. **A. Tran:** None. **J. Cashon:** None. **M. Garcia:** None. **R. Balmilero-Unciano:** None. **V. Salgado:** None. **D. Burbano:** None. **M. Wong:** None. **R. Lee:** None. **M. Iwashita:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.03/FF19

Topic: G.03. Motivation

Support: NIH Grant P20GM125508
Hawaii Community Foundation 18CON-90818

Title: Topological mapping and sparse modeling revealed the social-asocial transition of the brain transcriptome in the Mexican cavefish.

Authors: ***M. IWASHITA**[1], F. NASRIN[2], M. YOSHIZAWA[1];
[1]Sch. Life Sci., [2]Dept. of Mathematics, Univ. of Hawaii at Manoa, Honolulu, HI

Abstract: Visualization and extracting of meaningful representation of high dimensional data (ex. 30,000 genes or 300 metabolites) is challenging. Principal component analysis (PCA) and other modern methods (ex. t-SNE) have their own shortcomings—PCA has a trade-off between information loss and dimension reduction. Also, t-SNE visualization neither preserves distances nor the density of clusters. Therefore, these methods provide a hurdle in interpreting the gene regulation transitions from one cluster to another, where the clusters represent different biological states. Besides visualization, high-dimensional data has another major challenge in identifying the factors (genes) that are associated with the trait of interest (e.g., social affinity score). The challenge is due to high dimensionality compared with low sample sizes (ex. 30,000 genes vs. N=100)—overfitting in the model. Here we propose to use the combination of (1) topological mapping for visualization and (2) sparse modeling for finding the trait-associated factors. Topological mapping visualizes the complex data into nodes and links between nodes, where each node consists of multiple samples/individuals whose gene expression patterns are similar. This method allow us to quantify the transitions between clusters. The sparse modeling, based on Lasso and Ridge regressions, assumes that not all but a part of the variables (genes) explain the trait; therefore, does not require many samples for predicting coefficients. For the application of this method, we use the Mexican tetra, *Astyanax mexicanus* consisting of the social riverine (surface fish) and asocial cave populations (cavefish). Our team revealed that social affinity is still inducible in the asocial cavefish under a month of the ketogenic diet (KD)

treatment. Topological mapping successfully revealed the transition of how the KD treatment brought the cavefish-type brain gene expression close to the surface fish-types. Sparse modeling identified only several genes as significant predictors for social affinity, that responded to the KD treatment. These are the best candidates for the CRISPR/Cas9 cavefish knockouts which could stay asocial even after the KD treatment. We will also present another application of this pipeline to gut microbiota data.

Disclosures: **M. Iwashita:** None. **F. Nasrin:** None. **M. Yoshizawa:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.04/Web Only

Topic: G.03. Motivation

Support: American Epilepsy Society Seed Grant 873657

Title: Nest CO_2 preferences elucidate potential excitation-inhibition differences in African naked mole-rat subgroups.

Authors: A. GUADAGNINO[1], *D. MCCLOSKEY[2];
[1]CUNY Neurosci. Collaborative, Grad. Ctr. of City Univ. of New York, New York, NY; [2]Col. of Staten Island, City Univ. of New York, Staten Island, NY

Abstract: The existence of a durable, defensible nest is common to all eusocial species, including African Naked Mole-rats (NM-Rs). Previously, we have proposed that the NM-R colony nest environment helps to counteract native NM-R brain hyperexcitability, in part due to its high atmospheric carbon dioxide (CO_2) from the expired air of colony mates. The current project examined the causal relationship between the amount of expired CO_2 and specific nesting patterns of two main subgroups of non-breeding NM-R colony members: large workers (LW) and small workers (SW). The purpose of this project is to examine the optimal environmental conditions for nesting and brain excitatory-inhibitory balance in these two subgroups. Based on our previous observations of differences in colony behavior and inhibitory tone between SW and LW subgroups, we hypothesize that the optimal CO_2 for nesting will vary. To elucidate these differences, each subgroup was segregated from the colony and returned to a renewed environment where we observed activity and nest chamber CO_2 levels. We also measured latency to nest. The results demonstrate a significant difference between the number of inactive SW and inactive LW NM-Rs under low CO_2 conditions, with SW more likely to display inactive nest-initiating behavior under these conditions. Furthermore, the majority of LW subgroup members displayed significantly longer latencies to nest when CO_2 was low compared to the SW subgroup. These findings suggest that CO_2 drives the differences in behavioral phenotypes of each subgroup and indicate a heightened need for elevated nest CO_2 among larger colony

members. Future investigation of subgroup differences in basal metabolism and the capacity to generate CO_2 will be considered.

Disclosures: **A. Guadagnino:** None. **D. McCloskey:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.05/FF20

Topic: G.03. Motivation

Support: KAKEN 22K07336
KAKEN 22K07608
KAKEN 22H02812
KAKEN 18K07401
ISHIBASHI FOUNDATION

Title: Is the attractiveness of male mice from female mice inherited?

Authors: *Y. OHNISHI, Y. KAWAHARA, Y. H. OHNISHI, A. NISHI;
Dept. of pharmacology, Kurume Univ. Sch. of Med., Kurume, Japan

Abstract: Our study aims to unravel the mechanisms underlying female mate selection in male mice, with a particular focus on the inheritance of male attractiveness. Previous reports have highlighted the importance of appearance in the mate selection process. However, it remains unclear whether these factors, along with other potential determinants, are inherited. Our preliminary findings, previously reported at the Society for Neuroscience (SfN) conferences in 2017 and 2018, established reliable methods for identifying the most attractive male mouse among a group of four candidates. Notably, female mice exhibited consistent preferences for attractive males, regardless of variables such as estrous cycle, genetic background, age, sexual experience, and reproductive history. These observations strongly suggest the involvement of factors beyond these known variables in male attractiveness. In further studies presented at SfN 2019, we explored the influence of skinhead hairstyles on male mouse attractiveness and found no significant impact on female mate preference. Additionally, we recently examined the role of coat color in male mouse attractiveness, specifically comparing white and black mice. Our results revealed no conclusive difference in female preference between the two colors. Intriguingly, when male mice were concealed behind four layers of breathable filters, female mice were unable to select attractive males. Moreover, genetically blinded female mice displayed divergent preferences for the same male mice, indicating the presence of non-obvious cues in mate selection. To delve deeper into the inheritance of male mouse attractiveness, our proposed methodology involves mating two female mice each week and monitoring their birthing rates. Subsequently, we will assess the degree of attractiveness in the resulting offspring as they mature, utilizing established assays employed in our previous studies. Through this generational

analysis, we aim to elucidate the potential contribution of inheritance to male mouse attractiveness. In summary, our study seeks to unravel the mechanisms of female mate selection and investigate the inheritance of male mouse attractiveness. By employing rigorous methodologies and leveraging our current understanding of mate preferences in mice, we aim to uncover the complex interplay between genetics, behavior, and mate selection. The insights gained from this research will not only enhance our understanding of mouse biology but also contribute to broader knowledge of reproductive and evolutionary processes across diverse species.

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Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.06/FF21

Topic: G.03. Motivation

Support: 15H05724 to SO
22H02941 to SO
23KJ0281 to LK

Title: Differential role of estrogen receptor β in the medial amygdala in mate preference and lordosis in female mice

Authors: *L. KOGURE[1], T. MURAKAWA[2], T. HATSUKANO[2], S. TAKENAWA[2], M. MORISHITA[3], H. ISHII[3], M. NAKATA[2], S. OGAWA[2];
[1]Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; [2]Lab. Behavioral Neuroendocrinology, Univ. of Tsukuba, Tsukuba, Japan; [3]Anat. and Neurobiology, Grad. Sch. of Med., Nippon Med. Sch., Tokyo, Japan

Abstract: During the estrus phase, female mice exhibit both a high level of lordosis, which is a receptive posture for male mounting, and mate preference, which involves approaching and sniffing sexually active males over non-active males. The hormone 17β-estradiol (E_2), produced by the ovaries, is crucial in regulating these sexual behaviors in females by acting through two types of estrogen receptors (ER), namely ERα and ERβ. Previous research has indicated that E_2 primarily affects lordosis through ERα (Ogawa et al., 1998; Musatov et al, 2006), but the mechanism behind estrogenic modulation on mate preference in female mice remains unclear. Since ERβ-expressing neurons in the medial amygdala (MeA) have been found to play a role in male mice's preference for receptive females (Nakata et al., 2016), we have hypothesized that a similar mechanism may also be involved in mate preference in female mice. In the present study, we examined the role of ERβ in the MeA in the regulation of mate preference and lordosis behavior in female mice with the use of adeno-associated viral (AAV)-mediated RNA interference methods. Ovariectomized adult female C57BL/6N mice with hormone priming (see

below) were screened for mate preference. Only mice that showed a preference toward a gonadally intact male over a gonadectomized male were used in the subsequent analysis. Female mice were injected bilaterally with either AAV-ERβ-shRNA (MeAβKD) or AAV-Luc-shRNA (control) in the MeA. After two weeks of recovery period, all mice were weekly tested for mate preference three times: with subcutaneous injections of sesame oil (0.1 ml; 48, 24, and 3~4 h before the test) for week 1, and estradiol benzoate (5 µg/0.1 ml oil; 48 and 24 h before the test) and progesterone (250 µg/0.1 ml oil; 3~4 h before the test) for week 2 and 3. The results showed that the control group exhibited preference for sexually active males over non-active males, while the MeAβKD group did not show any preference. In week 3, all mice were also tested for lordosis behavior at 2hr after mate preference test and both groups displayed similar levels of lordosis behavior. Immunohistochemical analysis confirmed a significant reduction of ERβ-expressing cells in the MeAβKD group compared to the control group (approximately 70% down vs control). These findings suggest that E_2 action through ERβ in the MeA is necessary for females' mate preference but not for lordosis expression. Further analysis is being conducted to understand the specific behaviors related to sniffing and approaching males during the mate preference test. Supported by 15H05724 and 22H02941 to SO.

Disclosures: **L. Kogure:** None. **T. Murakawa:** None. **T. Hatsukano:** None. **S. Takenawa:** None. **M. Morishita:** None. **H. Ishii:** None. **M. Nakata:** None. **S. Ogawa:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.07/FF22

Topic: G.03. Motivation

Support: 21J10590 to TM
15H05724 to SO
22H02941 to SO

Title: Modulatory role of neuronal activity of Estrogen receptor β-expressing cells in the Dorsal raphe nucleus in the regulation of lordosis expression in female mice.

Authors: *T. MURAKAWA[1,2], L. KOGURE[2], K. HATA[2], S. TAKENAWA[2], K. SANO[2], S. OGAWA[2];
[2]Lab. Behavioral Neuroendocrinology, [1]Univ. of Tsukuba, Tsukuba, Japan

Abstract: Sexual receptivity in female mice, characterized by lordosis behavior, is prominently observed on the day of fertile ovulation, but significantly declines on subsequent days. Estradiol (E2) and estrogen receptors, ERα and ERβ, play important roles in the regulation of lordosis during the estrous cycle. Previous studies have shown that site-specific knockdown of ERβ in the dorsal raphe nucleus (DRN) does not affect lordosis expression on the day of ovulation but prevents its decline on the day after ovulation (Sano et al., 2018). In the present study, we

investigated the impact of neuronal activity of ERβ-expressing cells in the DRN (DRNERβ cells) on the levels of lordosis. Ovariectomized female mice from ERβ-iCre line were transfected with chemogenetic receptors for either inhibition (hM4Di) or facilitation (hM3Dq) of neuronal activity in the DRN in Cre-dependent manner, or with control viral vectors. All females were primed with estradiol benzoate 48 hours and 24 hours before the first behavioral test, conducted on two consecutive days. Day 1 test was done at 4 hours after progesterone injection, as the day of ovulation, and Day 2 test done 24 hours later, as the day after ovulation. Mice were injected with either Clozapine N-oxide (CNO) or saline injection 15min before behavioral tests. All groups exhibited higher levels of lordosis on Day 1 compared to Day 2 when they were tested with saline injection. Interestingly, CNO injection in hM4Di-treated mice on Day 2 prevented the decline of lordosis, whereas CNO injection in hM3Dq-treated mice reduced lordosis levels even on Day 1, compared to CNO injected mice treated with control virus. Additionally, we employed fiber-photometry recording to examine the neuronal activity of DRNERβ cells during mating behavior. On Day 1, thrusting stimuli from male mice inhibited neuronal activity in DRNERβ cells, while it tended to excite activity on Day 2. Furthermore, we investigated the efferent projections of DRNERβ cells and found dense signals in axon terminals in the anterior olfactory nucleus (AON), olfactory tubercle (OT), and ventral tegmental area (VTA). Finally, to explore the impact of neuronal activity in DRNERβ cells, we quantified the number of c-Fos-immunoreactive cells in entire forebrain regions. We found that DREADD induced excitation of DRNERβ cells resulted in c-Fos expression in both the projecting regions of DRNERβ cells and non-projecting regions including the medial preoptic area (MPO). Our findings suggest that the excitation of DRNERβ cells may be responsible for the decline in lordosis expression on Day 2, by influencing activity of the MPO via the AON, OT, and/or VTA.

Disclosures: **T. Murakawa:** None. **L. Kogure:** None. **K. Hata:** None. **S. Takenawa:** None. **K. Sano:** None. **S. Ogawa:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.08/FF23

Topic: G.03. Motivation

Title: Brain-wide neural mechanisms enhancing maternal behavioral response to infant cues

Authors: *B. R. MCRAE[1], A. LAWEN[1], L. HAMMOND[2], D. LICHTMAN[1], J. NAZARIAN[2], I. KAHN[3], B. J. MARLIN[4];
[1]Dept. of Neurosci., [2]Zuckerman Inst., [3]Dept. of Neuroscience, Zuckerman Inst., [4]Dept. of Neuroscience, Dept. of Psychology, Zuckerman Inst., Columbia Univ., New York, NY

Abstract: From the moment of giving birth, a mother must quickly adapt to the new demands of motherhood, attending to signals from her offspring and using them to inform her behavior. The brain’s adaptability to motherhood is of the utmost importance: maladaptive responses to infant

cues have been associated with neurological changes impacting both mother and child, including disorders such as postpartum depression. Research in rodents has begun to disentangle innate and learned features of the neural circuitry underlying maternal responses to infant cues. For example, distress vocalizations emitted by isolated mouse pups, termed pup calls, elicit maternal behavior and time-locked neural activity in the left primary auditory cortex (A1) in mothers, but not pup-naïve virgin females. However, naïve virgins are primed with innate neuronal tuning to a narrow range of pup calls, which broadens with pup care experience to allow for more reliable caregiving and pup call-evoked A1 responses. Prior work has shown that this increase in pup call salience in left A1 is facilitated, at least in part, by the neuropeptide oxytocin, but it is still unknown whether other brain regions exhibit similar experience-dependent, oxytocin-mediated plasticity to support maternal behavior. We aim to uncover the brain areas responsible for enhanced behavioral responses to pup calls in mice with maternal experience, and the role of oxytocin in the plasticity of these regions. We have used whole-brain activity mapping via immediate early genes and functional magnetic resonance imaging (fMRI) in mothers and naïve virgins to characterize the experience-dependent representation of pup calls throughout the brain. We conducted a Y-maze behavioral assay to confirm that mothers, but not naïve virgins, exhibit a preference for pup calls (mothers: $p=0.0195$, $n=10$; naïve virgins: $p=0.7695$, $n=10$; within-group Wilcoxon signed rank tests). We developed an fMRI setup to facilitate whole-brain mapping and behavioral monitoring of awake animals presented with ultrasonic auditory stimuli. Our findings reveal experience-based differences in pup call-evoked c-Fos expression and blood oxygenation level-dependent (BOLD) responses. Future work will investigate the necessity of oxytocin in maternal care learning and brain-wide sensitization to pup calls. Altogether, this work takes advantage of whole-brain imaging methods to identify brain regions that exhibit experience-dependent representations of pup calls, a stimulus that is crucial to mother-child communication and maternal behavior.

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Poster

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Program #/Poster #: PSTR096.09/FF24

Topic: G.03. Motivation

Support: NIMH funding R00MH124435

Title: Mapping the social brain: investigating competition behavior through c-fos expression in mice

Authors: *C. DE PAULA CUNHA ALMEIDA, A. LI, E. WRIGHT, A. CHAMBERS, M. CUM, R. IWATA, J. SANTIAGO PEREZ, N. PADILLA-COREANO;
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Abstract: In social species, survival and success hinge on complex group dynamics. A fundamental way in which social species interact is via competitive behaviors which shape their group dynamics into dominance hierarchies. Mice form social hierarchies in lab setting, making them a good model for studying the neural circuits underlying social competition behavior. This study aimed to identify differences in brain activity associated with social competition to direct future investigation of the neural mechanisms that drive competitive interactions. To investigate this, we employed a reward-based social competition assay to simulate competitive scenarios between mice in an operant chamber. The assay required two mice to be present in the chamber simultaneously, where they would compete for a food reward associated with an auditory cue. This setup ensured that the mice had to engage in direct competitive interactions for access to the reward. We examined c-Fos immunoreactivity, a marker of neuronal activation, across brain regions implicated in social behaviors. CD-1 adult male mice (n=14) were trained to associate an auditory cue with a food reward. Immediately prior to perfusions, half of the mice engaged in the reward-based competition assay, while the other half received cues and rewards in isolation as a control. To assess brain activity, we focused on key brain regions: the medial prefrontal cortex (mPFC) regions, including the infralimbic cortex (IL), anterior cingulate cortex (ACC), and prelimbic cortex (PL), as well as subcortical regions, the basolateral amygdala (BLA), mediodorsal thalamus (MD), lateral hypothalamus (LH), and ventral CA1 of the hippocampus (vCA1). Preliminary findings from our study revealed that all subregions of the mPFC exhibited increased c-Fos expression during social competition compared to the condition in which mice received the reward alone. Although we did not observe overall differences in c-Fos expression in subcortical regions between the two conditions, we found a correlation between social rank and c-Fos expression in the MD and BLA. These initial results align with previous studies, emphasizing the role of the mPFC in social competition behavior while also indicating that inputs from the MD and BLA may contribute to neural dynamics reflecting social rank. To further deepen our understanding, future experiments could employ electrophysiological recordings to reveal distinct activation patterns within these brain regions. Additionally, optogenetic manipulations targeting the MD-mPFC and BLA-mPFC pathways may provide valuable insights into their specific roles in social competition and rank.

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Poster

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Title: Probing the behavioral and neural dynamics of social satiety

Authors: *N. R. MACK, T. MINAKUCHI, S. N. OLINE, A. FALKNER;
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Abstract: While much attention has been paid to understanding how mesolimbic dopamine (DA) circuits drive learning to acquire specific rewards ("reinforcement learning"), we understand far less about how the brain constructs multiple competing representations of primary reward that drive this learning process. These representations of primary reward likely reflect the homeostatic nature of reward satiety. Here, we test behavioral predictions of homeostatic reinforcement learning in a social context using a novel behavioral task in mice that allows an individual to choose between two disparate social rewards: a same-sex conspecific or an opposite-sex conspecific. This task, termed 2-choice Social Operant with Automated Reward (SOAR), allows animals to roam between two chambers, each outfitted with two nosepoke ports (a "social" port and a "null" port). Activating the social port in a chamber activates the automated delivery of a social reward from above for a fixed interaction duration, and then automatically retracts the reward. Mice are tracked in 3D using a multi-camera system. We find that both male and female mice readily learn this task, showing preference for the social port over the null port in each chamber, and make numerous successive switches between the two distinct social rewards. We ask whether moving towards the homeostatic set-point via increased social "consumption" for one reward affected choice behavior for the other social reward in a satiety experiment by increasing the interaction duration for one social rewards at a time using a block design. In male mice, we observed that increasing the interaction time for either social reward reduced the poke rate and repetitive seeking ("stay trials") of that reward without affecting seeking for the other social reward, suggesting independence of social drives. In contrast, females are both less sensitive to this satiety manipulation and exhibit less drive independence. Dopaminergic activity in the nucleus accumbens (NAc) has been shown to increase during interaction with both same and opposite-sex rewards and individuals may choose to optimize their social rewards by "switching" when they become sated. To test whether DA activity in the NAc predicts state-dependent behavioral switches between two disparate social rewards in the SOAR task, we employ the GRAB-DA biosensor and fiber photometry and use an encoding model to disentangle the contributions of behavior. Together, these experiments unveil how manipulating social satiety for distinct social rewards affects social seeking in sex-dependent manner, and the role of mesolimbic DA in driving the switch between seeking disparate social rewards.

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Poster

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Title: Large-scale updating of excitatory and inhibitory population dynamics in a social brain network for aggression

Authors: *J. M. IRAVEDRA, E. M. GUTHMAN, A. L. FALKNER;
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Abstract: Prior social experience shapes future social decision-making. In many species, the experience of winning fights can lead to several behavioral changes, including increased and more effective aggression. However, the extent of these changes and what neural mechanisms instantiate them remain elusive. Here, we applied a multi-region fiber photometry strategy to map experience-dependent changes in the activity and connectivity of a large-scale brain network. This network is composed of brain regions involved in limbic processing such as the nucleus accumbens (NAc), the lateral habenula (LHb) and the infralimbic cortex (IL) as well as regions involved in motivating and/or patterning social actions like the medial preoptic area (mPOA), ventral lateral septum (vLS), bed nucleus of the stria terminalis (BNST), anterior hypothalamus, ventrolateral ventromedial hypothalamus (VMHvl), ventral premammillary nucleus, medial and posterior amygdala (MeA and PA), and periaqueductal gray. We tracked changes in putative excitatory and inhibitory cell population activity (vgat- and vgat+ respectively) across these regions using dual color imaging in adult male CD1 mice as they acquired aggression experience in a longitudinal resident-intruder paradigm. We found that, as animals became more engaged in aggression, so too did a majority of excitatory and inhibitory nodes across the network. Moreover, experienced animals displayed region-specific shifts in the level of excitatory versus inhibitory local population activity. Specifically, during the onset of aggression, regions like VMHvl, mPOA, vLS and BNST increasingly favored excitatory activity while regions like MeA, LHb and IL increasingly favored inhibitory activity. Further, using a regression-based approach to model cross-regional connectivity, we observed that experience correlated with increased functional decoupling of select excitatory populations (like that of VMHvl) from inhibitory ones (like that of mPOA and vLS). Lastly, experience was underpinned by region- and population-specific shifts in the lead-lag relationship of select network circuits. One such change involved the response timing of limbic circuits like the IL and NAc, which increasingly led to the activation of hypothalamic circuits like VMHvl and mPOA in later trials of aggression. Altogether, our findings suggest a network-wide mechanism for experience-dependent change in which aggression alters both the local and long-range balance of excitatory versus inhibitory activity, and shifts the temporal relationship of limbic forebrain and social hypothalamic circuits.

Disclosures: **J.M. Iravedra:** None. **E.M. Guthman:** None. **A.L. Falkner:** None.

Poster

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Title: Thalamic-hippocampal interplay in self-harm and aggression

Authors: I.-J. YOU, Y. BAE, ***S. SHIN**;
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Abstract: Self-harm and aggression are prevalent among teenagers exposed to early life trauma (ELT). Growing evidence indicates that self-harm and aggression co-occur, which has been termed “dual-harm”, yet we know far less about the neurobiological underpinnings of dual-harm and how they adapt in response to ELT. We found that systemic injection of L-type calcium channels (LTCCs) agonist, Bay K 8644, elicits dual-harm in mice in a dose-dependent manner. Moreover, we found that young adult mice exposed to ELT (e.g., infant-mother/littermate separation for 23 hr at postnatal day 3) show increased vulnerability to dual-harm. The thalamic nucleus reuniens (RE) contains vGlut2-positive neurons highly expressing LTCCs. Using in vivo calcium imaging, we have demonstrated that vGlut2 RE neurons in animals exposed to ELT show sensitized activity during self-biting behaviors. We also identified that ventral hippocampus (vHip)-projecting vGlut2 RE neurons send axon collaterals to other brain areas, including mPFC. Using chemogenetic manipulation, we found that the activation of vHip-projecting vGlut2 neurons, but not mPFC-projecting vGlut2 RE, increases the vulnerability to dual-harm. In addition, optogenetic inhibition of the vHip-projecting vGlut2 neurons normalized the exacerbated dual-harm in ELT mice. We propose that LTCC signaling in the downstream target-defined vGlut2 RE circuit is a primary biological substrate that mediates the occurrence of dual-harm. These results transform our understanding of self-harm and aggression, which will provide new insight into the circuit-specific roles of vGlut2 RE neurons in driving the risk of dual-harm in numerous psychiatric diseases.

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Poster

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Title: Chemogenetic manipulations of the brain oxytocin system alters juvenile social play behavior in a sex-specific manner

Authors: *S. M. BOWDEN[1], K. D. BECKER[2], M. G. HENRY[2], A. SHEMKE[1], V. GRINEVICH[3], A. H. VEENEMA[1];
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Abstract: Social play is a highly motivated and rewarding behavior primarily displayed during the juvenile period of many mammalian species. While participation in social play aids in the development of social competence and flexibility, deficits in social play, as seen in some autistic children, may contribute to life-long social impairments. Additionally, autistic individuals are more likely to view social interactions as less pleasurable. The brain oxytocin (OXT) system is considered a potential therapeutic to improve social interaction in autistic individuals, however little is known about the role of OXT in social play. To fill this gap, we first determined the involvement of OXT produced in the paraventricular nucleus of the hypothalamus (PVN) in the regulation of social play behavior in male and female juvenile Wistar rats. Briefly, an excitatory DREADD construct under the control of the OXT promoter was infused into the PVN. One week later, social play behavior was assessed over two trials, in which either clozapine-*N*-oxide or saline was administered prior to testing. A significant sex x drug interaction was found in the PVN, in which chemogenetic stimulation of PVN^{OXT} cells decreased social play duration in males while females showed a strong trend towards an increase in social play duration. Next, we examined the involvement of PVN^{OXT} projections to a downstream target, the nucleus accumbens (NAc). The NAc is well known for its role in the regulation of reward, and here we confirmed that the NAc receives OXTergic projections from the PVN in both male and female juvenile rats. Using the same excitatory DREADD combined with cannulation of the NAc, we were able to specifically target and stimulate PVN^{OXT} terminals within the NAc. However, we found no effects of terminal stimulation of PVN^{OXT} axons in the NAc on social play. One reason could be oversaturation of OXT within the synapses of the NAc. Currently, we are investigating the role of OXT receptor (OXTR) expressing cells within the NAc in social play. Using OXTR-iCre rats and a cre-dependent inhibitory DREADD, we will determine the involvement of OXTR-expressing neurons in the regulation of juvenile social play, and whether this occurs sex specifically. In conclusion, we provide evidence for a sex-specific role of OXT in the regulation of social play behavior. This may have implications for the potential need for sex-specific use of OXT-based therapeutics to improve social play engagement in autistic children.

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Poster

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Topic: G.03. Motivation

Support: NIDA IRP

Title: Developing tools for studying neuronal ensembles that encode volitional social reward in mice

Authors: *S. S. LEE[1], M. VENNIRO[2], Y. SHAHAM[1], B. T. HOPE[1], L. A. RAMSEY[1];
[1]Behavioral Neurosci. Res. Br., NIDA IRP, NIH, Baltimore, MD; [2]Dept. of Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Background: We recently developed a mouse model of operant social self-administration and choice (Ramsey et al. Biol Psychiatry, 2021, Ramsey et al. Nature Protocols, 2023). Using this model, we found that outbred female CD1 mice, but not C57BL/6J female mice, showed reliable social interaction self-administration, strong social-seeking behavior during isolation, and preference for social interaction over food. Current neurobiological investigations of social behavior are performed almost exclusively using C57BL/6J mice, the most common background strain of transgenic mice. Given that female C57BL/6J mice are not suitable for studying operant social reward, we created new transgenic lines to study activity-dependent neuronal ensembles that encode social self-administration. We tested whether breeding outbred female CD1 mice with FosGFP, FosTRAP2, and FosTRAP2 x Ai14 transgenic C57BL/6J male mice will maintain the operant social reward phenotype in the hybrid F1 offspring.
Methods: First, we crossed male C57BL/6J transgenic mice from each of the three strains (FosGFP, FosTRAP2, FosTRAP2 x Ai14) with female CD1 mice. We trained the F1 generation to lever-press for palatable food pellets and then to lever-press under increasing fixed-ratio response requirements for access to a same-sex social partner. Next, we tested their motivation to seek social interaction after 15 days of social isolation. We compared these three transgenic strains on CD1 background to wild-type CD1 male and female mice.
Results: Male and female mice from the three newly bred hybrid transgenic mouse lines showed reliable social self-administration and social seeking after isolation, similar to wild-type CD1 mice.
Conclusion: Our data indicate that the social phenotype is maintained in the F1 generation in all three strains tested using the hybrid breeding scheme. This will enable us and other researchers, to identify, characterize, and manipulate activity-dependent neuronal ensembles involved in operant social reward.

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Poster

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Topic: G.03. Motivation

Title: Isolated, but not pair-housed, male and female rats demonstrate social conditioned place preference

Authors: *P. C. BENSING, C. P. BOWERS, B. IVERSON, K.-C. LEONG;
Psychology, Trinity Univ., San Antonio, TX

Abstract: Investigation of how various factors influence social reward salience has many important implications for the understanding of general reward processes. Factors such as individual or group housing conditions, in particular, may modulate social reward and are particularly relevant given variability of social interactions across animals and humans. The present study highlights the effect of paired or isolated housing conditions on social reward preference using a social conditioned place preference (CPP) paradigm with Sprague Dawley rats. All male and female rats were assigned a same-sex, similar weight pair to be conditioned with throughout the study. In the individual housing condition, rats were single-housed for 2 weeks prior to and throughout the experimental paradigm. Rats in the paired housing condition were housed with their assigned pair at least 2 weeks prior to and throughout the experiment. On the first day of the CPP paradigm, all rats were individually placed in the CPP apparatus for 15 minutes with free access to two chambers with distinct visual cues to obtain a baseline preference of both chambers. Rats were conditioned over the next 8 days, in which rats were placed on alternating days into either the social-paired chamber with their conspecific pair or the other chamber, alone. On the 10th day of the paradigm, the rats' chamber preference was retested and a comparison to the baseline preference allowed for determination of whether there was a significant establishment of social place preference. Our results demonstrate that both male and female rats established a preference for the socially-paired context when housed in isolation but not when pair-housed. These findings suggest that the rewarding effects of social interaction are dependent on housing conditions, specifically that social isolation may increase the salience of social reward. Subsequently, we examined the role of oxytocin receptors in the ventral tegmental area (VTA) in mediating this effect.

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Poster

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Title: The effects of endocannabinoid system activation through exercise on sociabilty in adolescent rats.

Authors: A. RODRIGUEZ-LEON[1], K. TORRES-MONTERO[1], A. ACEVEDO-JETTER[1], A. CORRETJER-DÍAZ[1], J. PADILLA-ESCALONA[1], D. UMAÑA[1], M. DUCHESNE-MENDOZA[1], S. SANTOS-DELEON[1], K. RODRIGUEZ-MORALES[1], *C. MALDONADO-VLAAR[2];
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Abstract: Several studies have found that the endogenous cannabinoid system (eCs) regulates some behavioral pathways that could help develop an adolescent into a functional adult. Some of these investigations have shown that an incrementation of anandamide (AEA), through the inhibition of fatty acid amide hydrolase (FAAH), is associated with increased sociability in adolescence. Other studies have shown that there is a correlation between exercise and increased anandamide in some areas of the brain. With this association, we hypothesized that, through an up-regulation of high levels of anandamide within the amygdala and the Nucleus Accumbens (NAcc), exercise will be increased, and there will be an increment of sociability in adolescent rats that exercise. Initially, we used sixteen Sprague Dawley male (16) rats that were divided into sedentary and exercise groups. These groups were further subdivided into four (4) groups, where two groups received vehicle or treatment of the inhibitor of FAAH, URB597 (0.1 mg/kg, i.p) and wheel running exercise for ten (10) consecutive days, and the other two groups received vehicle or URB597 while being sedentary. On the last day of the experiment, the rats were submitted to a sociability test for (15) minutes in which behavioral parameters like pinning and contact behavior were recorded. At the end of the sociability test, animals were euthanized, and the brains were collected for histological purposes. Brain regions such as the amygdala and Nacc were selected for future biochemical analysis. Preliminary results revealed that non-sedentary animals exposed to URB597 treatment exhibited an increase in exercise behaviors. With regards to sociability scores, rats that exercised showed more social behavior parameters when compared to the sedentary groups. The present study suggests that exercise seems to be increased in adolescent rats that were treated with our target drug and exercise appears to be correlated with sociability in adolescent rats.

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Poster

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Title: Gonadal hormone coordination of social behavior and neural activity across the subcortical, social behavior network in adult mice

Authors: *E. M. GUTHMAN[1], J. M. IRAVEDRA-GARCIA[1], L. SIRRS[1], E. WANG[1], J. VAN VEEN[2], S. M. CORREA[2], A. L. FALKNER[1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: Gonadal hormones powerfully modulate social behavior. However, we lack a mechanistic understanding of how they coordinate behavioral change through networks of hormone-sensitive neurons found across the brain. Here, we develop a comprehensive high-throughput behavioral, neural, and transcriptional recording strategy to determine: 1) which behaviors are under hormonal control, 2) whether changes in neural activity across a hormone sensitive brain network correlate with this behavioral plasticity, and 3) whether gonadal hormones are sufficient to drive transcription in these hormone-sensitive networks, acting as a potential neuroendocrine mechanism mediating this plasticity. We record longitudinally before and after gonadectomy (GDX) across sexes to compare these profiles in an “high” and “low” hormone state. First, we generate computational pipelines for behavioral discovery and holistic behavioral quantification using pose tracking and unsupervised clustering to compare behavior across a change in hormone state. We find GDX reorganizes expression of asocial and proactive social behaviors more than reactive social behaviors. Overall, GDX changes behavioral expression more during same-sex interactions compared to opposite-sex interactions and leads to greater changes in male compared to female behavior. Second, we design methods for simultaneous two-color imaging of neural activity in identified populations across hormone-sensitive regions of the subcortical social behavior network (SBN). We use Esr1-Cre mice to express cre-dependent jRCaMP1b in hormone-sensitive, estrogen receptor alpha (ERa) expressing neural populations and cre-excluding GCaMP6f in ERa- populations in 11 SBN regions. We find ERa+ populations show higher activity for proactive social behaviors compared to ERa- populations prior to GDX. Further, GDX drives brain region-specific changes in behavior-correlated population activity, suggesting coordinated SBN activity may be necessary for the execution of these behaviors. Finally, to uncover a potential mechanism by which a hormone state change may alter neuronal activity, we record a novel fluorescent reporter of ERa-driven gene expression (SeeER) in the 11 SBN regions across a multi-day timescale. Preliminary results demonstrate both estradiol and testosterone drive transcription via ERa in a subset of the SBN regions that encode proactive social behaviors.

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Poster

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Title: Changes in social rank flexibly update behavioral and neural responses to social cues

Authors: *D. BLACKMAN[1], O. C. TIMMERMANS[1], S. N. OLINE[1], A. P. FINK[3], C. E. SCHOONOVER[4], A. L. FALKNER[2];
[2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [4]Neurosci., [3]Columbia Univ., New York, NY

Abstract: Across social species, groups of individuals frequently exhibit hierarchical social organization. High rank animals use a well-characterized suite of social behaviors and chemosensory cues to assert their status, thus gaining preferential access to limited resources. Though hierarchies are typically stable, social rank is not fixed: an individual can rise or fall in the hierarchy depending on changing social and environmental circumstances. Therefore, we define rank as a flexible state that patterns broad sets of actions in response to social stimuli, and hypothesize that changes in rank can re-pattern these behavioral responses. Using a novel assay that allows precise millisecond-level monitoring of behavioral engagement, aversion, and arousal to chemosensory social stimuli (urine), we find that low-ranking males exhibit multidimensional avoidance phenotypes during cue exposure significantly more than high-ranking males. To test whether these behaviors are updated after experience, we shuffle the animals into new hierarchies and show that animals update their behavioral responses to reflect their new social status. The ventral premammillary nucleus (PMv), a hypothalamic node in the social behavior network that richly expresses androgen receptors (ARs), has previously been implicated in both male conspecific aggression and sensory processing, making it well-poised to integrate incoming sensory information and influence rank-specific behaviors (Stagourakis et al. 2018; Chen et al. 2020). To test whether the PMv encodes a flexible representation of social rank, we performed chronic in vivo electrophysiology using multi-shank silicon probes, measuring single unit activity in the PMv across time as animals underwent rank change. A subpopulation of PMv single units that are responsive to urine cues change response properties after either a change in individual rank or hormone state. In addition, we find that genetic deletion of AR in the PMv during adulthood or chemogenetic suppression of a subpopulation of PMv neurons promotes a range of “subordinate-like” behaviors. Taken together, these findings suggest a role for an androgenic mechanism in the PMv for mediating flexibility and stability of social rank.

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Poster

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Title: Rank and sex influence olfactory-guided social motivation

Authors: ***E. RODRIGUEZ**[1], C. ADEYEMI[2], B. A. UCEDA-ALVAREZ[2], D. SALZMAN[3]; [1]Zuckerman Inst., [3]Neurosci., [2]Columbia Univ., New York, NY

Abstract: Organisms must learn to evaluate and respond to environmental stimuli that indicate appetitive or aversive events. These decisions are influenced by dynamic and complex social interactions. Social interactions rely on a subject's ability to represent sensory information about social agents, assign social meaning to these neural representations, and guide emotionally motivated behavioral responses. How social information directs behavior and emotions remains poorly understood, as we lack mechanistic insight into the neural pathways mediating the conversion of sensory representations to socially driven behavior. Our experiments focus on how the hierarchical rank of individuals influences motivational behavior. To obtain experimental control of social stimuli that drive behavior, we assessed how urine sample odors from dominant and submissive mice influenced the behavior of intermediate ranked mice. The results implicate that this olfactory-guided behavior is both rank-dependent and sex-specific. These findings provide a springboard for deciphering the role of the anterior cingulate cortex and basolateral amygdala in contributing to sex-dimorphic olfactory-guided motivational and social behaviors.

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Title: Partner loss enhances partner seeking behavior and dopamine receptor expression in select brain regions in female prairie voles

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Abstract: The loss of a meaningful attachment figure is considered a traumatic event and may impact various cognitive processes, such as motivational processing, and the psychological health of an organism. In humans, the grieving process is characterized by intense sadness, intrusive thoughts of the deceased, and an intense yearning or longing for reunion with the deceased (Bonanno et al. 2002). Human fMRI studies have shown hyperactivity in emotional pain and motivational centers of the brain when an individual is reminded of a lost romantic partner (Acevedo et al. 2012; O'Connor et al. 2008; Gundel et al. 2014), but the molecular underpinnings of these changes in activity are unknown. The monogamous prairie vole (*Microtus ochrogaster*), which establishes lifelong social bonds between breeding pairs, known as *pair bonds*, display distress and shifts in motivational states which promote partner seeking during prolonged periods of pair separation or loss, providing a model to investigate behavioral and molecular changes following the loss of this meaningful attachment figure. To study the behavioral changes associated with motivational systems, we used a novel odor preference test to assess partner-seeking behavior and the sucrose preference test to assess non-social, reward-driven motivation. One week following the loss of a partner, females that lost a male partner investigated their partner's odor significantly more than females that lost a female cagemate or remained intact with a female cagemate or a male partner. Moreover, in an odor preference test for stranger odors, females that lost a male partner also demonstrated increased investigation of the stranger odor. There were no changes observed in the sucrose preference test, suggesting that partner loss may not significantly alter motivation for non-social stimuli, but does increase motivational behaviors towards general social cues. Additionally, western blotting revealed a significant increase in dopamine receptor type 1 (DRD1) concentration in the medial preoptic area (mPOA) in females that lost a male partner, as compared to all other groups. This increase was not seen in other regions associated with motivation and emotional processing. Dopamine signaling and DRD1 activity in the mPOA are primed by other socially rewarding stimuli, such as mother-infant interaction and sexual activity. Thus, these results may be indicative of a mechanistic relationship between mPOA DRD1 and partner seeking behaviors following loss in female prairie voles in which dopamine signaling in this region drives partner seeking during periods of loss with the goal of partner reunion.

Disclosures: A.C. Kirckof: None. **E.M. Vitale:** None. **A.S. Smith:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.21/GG11

Topic: G.03. Motivation

Support: NIMH Grant R01MH133123

Title: Opposite-sex pairing influences insular cortex activity and structural connectivity to the mesocorticolimbic dopamine system in male prairie voles

Authors: *E. M. VITALE, A. S. SMITH;
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Abstract: The prairie vole (*Microtus ochrogaster*) is a monogamous rodent species that has been used to study the neurobiological mechanisms of social behavior for over three decades due to their formation of selective, opposite-sex relationships known as pair bonds. Pair bonding in males and females is determined behaviorally by selective affiliation for a social partner over other conspecifics and intruder-directed aggression. It is well-known that the mesocorticolimbic dopamine (DA) system, with a particular focus on DA release in the nucleus accumbens (NAc) from the ventral tegmental area (VTA), is involved in the formation and maintenance of pair bond-induced social selectivity. Interestingly, male and female prairie voles also form peer relationships with familiar, same-sex cage mates with whom they are housed for extended periods of time. However, these peer relationships do not appear to be regulated by the mesocorticolimbic DA system, suggesting that structural and/or functional neural circuit selectivity could underly these two distinct relationship types. Additionally, these circuits could involve differential top-down regulation of the mesocorticolimbic system, though the role of higher-order cortical regions in prairie vole social relationships has been severely overlooked. The insular cortex (IC) is a key regulator of emotion in humans and has been implicated in rodent social decision-making and social preference. In this series of experiments, we used fiber photometry to assess activity of the genetically encoded calcium indicator GCaMP and the fluorescent DA sensor GRAB-DA in the IC during a series of familiar and novel social interactions in male prairie voles that were either housed with a same-sex peer or an opposite-sex mate. We also used cholera toxin B-conjugated retrograde tracers injected into regions of the mesocorticolimbic DA system (i.e. NAc, VTA) to determine whether same-sex or opposite-sex pairing influences structural connectivity and/or functional activity of IC neuron populations that project to different components of this system. With these experiments, we hope to gain new knowledge on potential upstream, higher-order cortical influences on the classically studied socio-motivational circuits that drive prairie vole social relationships and social selectivity.

Disclosures: E.M. Vitale: None. **A.S. Smith:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.22/GG12

Topic: G.03. Motivation

Support: NINDS/BRAIN Initiative RO1 NS113104

Title: Activity of the mesolimbic reward system in the formation of a pair bond and display of bond related behaviors in male and female prairie voles (Microtus ochrogaster)

Authors: *K. GOSSMAN, A. SMITH;
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Abstract: Many species live in complex social environments that require them to display context-appropriate behaviors during distinct social interactions to maintain social relationship. It is suggested that there are many benefits to the formation and maintenance of social relationships. Unlike other rodent models, the prairie vole (*Microtus ochrogaster*) is a socially monogamous rodent that forms pair bonds, or bonds between breeding pairs. Pair bonds in prairie voles are established and maintained, in part, by the display of context-appropriate behaviors including partner directed affiliation and aggression toward stranger conspecifics. The mesolimbic reward system has be proposed to be part of a social brain network which regulates these bond-related behaviors because of the reward of social attachment, along with the variety of behaviors this network regulates. Surprisingly, only a few mesolimbic regions have been studied in the context of vole pair bonding, with most work focused on the nucleus accumbens (NAc). However, it is suggested that circuits and networks regulate the display of commitment behaviors rather than one region. This research aims to assess how the ventral tegmental area (VTA), a theoretical hub of this network, influences pair bond formation and bond-related behaviors, including the regulation of neural activity of down-stream limbic regions such as the NAc, basolateral amygdala (BLA), and anterior cingulate cortex (ACC). Activation of the VTA in female voles with the use of a Gq DREADDs, inhibits the formation of a pair bond during a period sufficient for a bond to form. Second, with the use of the genetically encoded calcium indicator, GCaMP6f, and multichannel fiber photometry, we housed our subjects with a same-sex or opposite-sex conspecific for 24 hours, a sufficient period for voles to form a partner preference, then exposed them to their cagemate, a same-sex conspecific, and an opposite-sex conspecific. Currently, the data suggest bachelor male voles show lower levels of aggression toward opposite-sex conspecifics, where male voles housed with an opposite-sex conspecific show selective affiliation to their cage mate and selective aggression toward a stranger conspecific regardless of the sex. Furthermore, the BLA has increased activity during aggressive encounters, where the NAc seems to show increased activity during affirmative and aggressive interactions. We plan to incorporate males into our VTA bond formation study and incorporate female prairie voles and run lag-analyses on these four regions during the social encounters to assess circuits activity during affiliative and aggressive behaviors based on social status.

Disclosures: K. Gossman: None. **A. Smith:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR096.23/GG13

Topic: G.03. Motivation

Support: NIH MH125408
NIH MH109450

Title: Role of ten-eleven translocation 2 (tet2) in pair bonding in prairie voles

Authors: *M. CRAWFORD[1,3], F. DUCLOT[1,3], L. SAILER[1,3], A. AKBARABADI[1,3], I. ROWE[1,3], D. STEWART[1], Z. WANG[2,3], M. KABBAJ[1,3];
[1]Biomed. Sci., [2]Psychology, Florida State Univ., Tallahassee, FL; [3]Florida State Univ. Program in Neurosci., Tallahassee, FL

Abstract: Socially monogamous prairie voles form enduring social attachments, displaying a preference for their partner over a stranger and a selective aggression towards unfamiliar conspecifics. Epigenetic changes such as histone modifications and DNA methylation play an important role in the modulation and maintenance of gene expression and behavior. Here we examined the role of Tet enzymes, which are implicated in DNA demethylation, in pair bond formation and maintenance. We focused on the Nucleus Accumbens (NAc), which has been shown to play an important role in partner preference. Our data showed that Tet2 mRNA, but not Tet1 or Tet3, is upregulated in the NAc of pair-bonded female prairie voles after 2 weeks of cohabitation with a partner, compared to sexually naïve controls. However, there was no increase in Tet2 after 24hrs of cohabitation. These findings suggest that Tet2 may play a role in bond maintenance. We thus hypothesized that knockdown of Tet2 would impair bond maintenance. To test this, an AAV expressing either a Tet2-shRNA or a scr-shRNA was injected bilaterally into the NAc of female prairie voles. Three weeks after injections, the females were paired with a partner and later tested for partner preference. When given a choice between their partner and a stranger during a Partner Preference Test, female prairie voles that were injected with the Tet2-shRNA spent less time in side-to-side contact with their partner compared to controls. To determine if social recognition was impaired by the knockdown of Tet2, sexually naïve females received bilateral injections of either the Tet2-shRNA or scr-shRNA in the NAc and underwent a Peer Preference Test and a Social Discrimination Test. During the Peer Preference Test, subjects were given a choice between their cage mate since weaning or a novel animal. Females injected with the Tet2-shRNA spent less time with their cage mate and more time with the stranger compared to controls. Sexually naïve females injected with the Tet2-shRNA also displayed increased social novelty-seeking behavior compared to controls during the Social Discrimination Test, spending more time interacting with a novel than the familiar animal. Taken together, these studies suggest that Tet2 in the NAc plays an important role in pair bonding maintenance by reducing interest in novel male prairie voles.

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Poster

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Program #/Poster #: PSTR096.24/GG14

Topic: G.03. Motivation

Support: NINDS/BRAIN Initiative R01 NS113104
Fulbright Colombia

Title: Role of corticotropin releasing factor in social defeat and social attachment in the prairie vole (Microtus ochrogaster)

Authors: *L. NERIO MORALES[1], A. SMITH[2];
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Abstract: Chronic exposure to social conflict promotes the onset of social anxiety (SAD) in humans. SAD is characterized by generalized social avoidance, marked anxiety symptoms in social situations, and social attachment dysfunction. This is particularly relevant as intimacy and close relationships are critical components of human social behavior and an integral part of health and survival. While highly prevalent and incapacitating, the molecular mechanisms driving SAD effects on social attachment are unknown. Our lab has developed a chronic social defeat (SD) model using male and female prairie voles (*Microtus ochrogaster*) to study SAD and its effects on affiliation. Once defeated, prairie voles display social avoidance of strangers and anxiety-like behaviors, characteristic traits in human SAD. Using this model, we have recently documented that SD induces sex-dependent effects on social attachment, as it inhibits partner preference in males while accelerating it in females. Additionally, corticotropin releasing factor (CRF) neurons in the bed nucleus of stria terminalis (BNST) seem to play an important role in the mediation of these behaviors, as they are necessary for pair bond formation, and BNST CRF expression is affected by SD. Further, BNST CRF behavioral effects change from appetitive to aversive in response to stress and seem to vary in a sex-dependent manner. It is proposed that this may be due, in part, to a stress-induced shift in CRF regulation of dopamine transmission in the mesolimbic dopamine system, a circuit relevant for social attachment and pair bond formation. Here, we determine CRF projections from the BNST into the ventral tegmental area (VTA) to nucleus accumbens (NAc) circuit and elucidate their activity state in response to pair bonding in SD. Additionally, we determined the effects of pharmacological manipulation of CRF signaling directly into the VTA and the NAc to assess whether this manipulation prevents the behavioral effects observed in partner preference after SD. Our preliminary data indicate that inhibition of CRF R1 receptors in the VTA recovers partner preference in defeated male prairie voles, suggesting that the attachment deficits observed in SD are mediated by CRF signaling into the mesolimbic dopamine system.

Disclosures: L. Nerio Morales: None. **A. Smith:** None.

Poster

PSTR096. Motivation: Social Communication and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR096.25/GG15

Topic: G.03. Motivation

Support: NIH Grant NS113104-04
NIH Grant GM103418

Title: Medial amygdala and bed nucleus of the stria terminalis respond to learned avoidance of social stimuli in male prairie voles (Microtus ochrogaster)

Authors: *J. P. GOFF[1,2], M. C. TICKERHOOF[1,3], A. S. SMITH[1];
[1]Pharmacol. and Toxicology, The Univ. of Kansas, Lawerence, KS; [2]Natl. Inst. on Alcoholism and Alcohol Abuse, NIH, Rockville, MD; [3]Biol. Sci., Fordham Univ., Bronx, NY

Abstract: Social anxiety disorder (SAD) is characterized by a debilitating fear of social situations, with individuals overestimating the potential for social interactions to produce aversive outcomes. Social defeat stress (SDS) is an animal model used in preclinical research that simulates aversive social encounters and produces avoidance of novel social stimuli, similar to that seen in individuals suffering from SAD. Our lab has shown that the activity of dopamine receptor 1 (DRD1)-expressing neurons in the medial amygdala (MeA) regulate this learned social avoidance in prairie voles (*Microtus ochrogaster*). DRD1-MeA projections have also been shown to regulate innate predator fear in mice via an inhibitory projection from the bed nucleus of the stria terminalis (BNST) and an excitatory projection from the ventromedial hypothalamus (VMH). Here, we investigated the neural correlates of learned social avoidance using an odor exposure task and ex vivo analysis of brain activity. Male prairie voles underwent a three-day SDS protocol that involved exposure to an aggressive, same sex conspecific. Following SDS and one week recovery, subjects were presented with an odorant simulating either the presence of a predator or a novel conspecific. An additional group was presented with a non-salient control odor. Behavior and location in the arena, relative to the odorant, were manually scored for analysis. Following odor exposure, brains were collected for immunolabeling and quantification of c-Fos expression, a correlate of brain activity. Stress-naïve voles investigated the social odor more than the neutral or predator odors. However, voles previously exposed to SDS demonstrated an aversion to conspecific odor presentation compared to stress-naïve subjects, as measured by increased time spent in the area of the arena furthest from the odorant. Analysis of c-Fos expression, when normalized to the control odor, showed that MeA activation due to predator odor was significantly reduced in stress experienced animals. Additionally, expression of c-Fos in the BNST was significantly greater in stressed subjects presented with the novel social stimuli. These findings align with prior data implicating the MeA in approach/avoidance decision making and support the idea that an inhibitory BNST projection to the MeA promotes avoidance. The neural correlates identified here may be relevant to the etiology or expression of SAD and suggest circuit elements that could be targeted for therapeutic intervention. Ongoing work aims to further characterize this circuit by analyzing neurotransmitter phenotype of the proposed regions and their connectivity using CTB retrograde tracing.

Disclosures: J.P. Goff: None. **M.C. Tickerhoof:** None. **A.S. Smith:** None.

Poster

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Program #/Poster #: PSTR096.26/GG16

Topic: G.03. Motivation

Support: R01 MH12100 9

Title: Changes in gamma rhythm in the amygdala predict saccades in macaques during social gaze control

Authors: *Z. NADASDY[1,2,4], H. DORMÁN[3], S. LEE[5], K. M. GOTHARD[6];
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Abstract: Joint attention (JA) and gaze following (GF) are prerequisites of cooperative social interactions and social coordination in primates, including humans. They play fundamental roles in learning, understanding others' intentions, and communicating within the social hierarchy. The asymmetry between peers regarding JA and GF depends on social status. Yet the contribution of the amygdala to the underlying circuitry and neuronal mechanisms of social gaze control is unknown. We analyzed the time-frequency dynamics of the local field potentials (LFPs) recorded from the amygdala, hippocampus, entorhinal cortex, anterior cingulate, and various cortical areas by using linear arrays of electrodes while the subject monkeys watched videos of two other socially interacting monkeys. Our main findings were: (1) Transition of gamma-band oscillations between pre-saccade and post-saccade intervals is prominent in the amygdala and hippocampus during JA and GF. (2) The LFP from the amygdala displays a short (~100 ms duration) gamma power increase right before saccade onset, followed by a similar gamma power increase in the CA1 and CA3 areas of the hippocampus after saccades of GF and JA. (3) The strength of transition depends on the hierarchical status of the observing monkey. (4) Gamma power increases when the subject monkey makes a new saccade to a dominant monkey after fixating on a subordinate conspecific. (5) The effect was more robust relative to saccade onsets than relative to fixation onsets. The predictive coupling between increased gamma band activity in the amygdala and saccade initiation followed by post-saccade hippocampal engagement suggest a new functional conduit for social gaze control.

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Poster

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Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.27/GG17

Topic: G.03. Motivation

Support: NIH/NIDCD 04845 (LMR)
F30 MH122048 (KKS)

Title: Processing of Expression and Identity in Audiovisual Communication Stimuli by Ventral Prefrontal and Amygdala Neurons

Authors: K. K. SHARMA[1], M. A. CARDENAS[2], M. D. DILTZ[1], K. M. GOTHARD[2], *L. M. ROMANSKI[1];
[1]Neurosci., Univ. of Rochester, Rochester, NY; [2]Univ. Arizona, Col. Med., Tucson, AZ

Abstract: Facial and vocal expressions are a fundamental component of communication in primates. Accurate interpretation of an expression is a critical social function that relies on brain networks involved in face and vocal perception, multisensory integration, and emotion. In non-human primates, viewing an expression engages areas within the occipital and temporal lobes, the amygdala, and the ventrolateral prefrontal cortex (VLPFC). Previous studies of macaque face processing have utilized mainly static face images to investigate features relevant to social communication including identity, expression, valence, etc. In the present study we have, instead, used short videos of species-specific vocalizations with their accompanying facial expressions during recordings in the macaque VLPFC and in the amygdala. Since perception of identity and expression are critical social functions, we examined whether neural responses to naturalistic stimuli were driven by these two categorical features in the prefrontal cortex and in the amygdala. We recorded single neurons and ensembles in the VLPFC, using V-Probes (Plexon) and implanted micro arrays (Microprobes) in two subjects. In a third subject, V-probes were used to record single units and ensembles in the amygdala. All subjects viewed short videos of unfamiliar conspecifics making facial expressions of aggressive, affiliative, and neutral valence, accompanied by the appropriate vocalization. We analyzed the impact of identity and expression on neural firing rates from both regions with a two-way ANOVA. In the VLPFC, of 285 neurons responsive to our stimuli, 28% (80/285) had a main effect of identity, 19% had a main effect of expression, and 23% their interaction. In the amygdala, of 216 responsive cells, 18% had an effect of identity, 11% of expression, and 12% of their interaction. Further analysis determined that in VLPFC neurons, the decoding of expression and identity using single unit firing rates rendered poor accuracy; however, when decoding models were built using pseudo-populations, accuracy for both expression and identity increased with population size. Moreover, in VLPFC, peak decoding of identity was higher and occurred earlier than that for expression. Similar population analyses will be applied to amygdala recordings to determine if both VLPFC and amygdala neurons process social communication variables with a similar accuracy and time-course.

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Poster

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Topic: G.03. Motivation

Support: P50 MH100023
R01 MH121009

Title: Neurons in the amygdala of third-party observers of hierarchical social interactions respond to the status of the observed individuals

Authors: *S. LEE[1], U. RUTISHAUSER[3], L. J. YOUNG[4], K. M. GOTHARD[2];
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Abstract: Neuroimaging studies (Zink et al., 2008; Kumaran et al., 2016) in humans suggest that the amygdala and hippocampus respond to the social status of individuals acquired through transitive inference by observing dominant-subordinate interactions. We recorded single units from the amygdala and hippocampus of two adult male monkeys while they watched videos of simulated pairwise interactions between groups of 4 monkeys organized into virtual hierarchies. The dominant monkeys at the top of each hierarchy were shown threatening each of the other 3 animals, while the monkeys at the bottom were submissive to all social partners. The second and third-ranking monkeys were dominant or subordinate depending on the rank of their social partner. We asked, (1) whether the social status of the animals shown in the videos modulated the firing rate of neurons in the amygdala or the hippocampus, and (2) whether the social partner or the status differential between the pair of interacting animals was represented in any dimension of the recorded neural activity. We recorded 232 and 87 neurons from the amygdala and hippocampus, respectively. For each neuron, we quantified separately firing rates during fixations on the dominant and the subordinate monkeys. We found that 28% of cells in the amygdala and 13% of cells in the hippocampus responded differentially to the dominant and subordinate individual. In both the amygdala and hippocampus, the magnitude of neural responses elicited by the attended individual was modulated by the status of the unattended social partner, suggesting that in addition to the status of each individual, neurons respond to the status differential of pairs of animals (partner effect). A demixed principal component analysis (dPCA) determined the relative contribution of the social status of the fixated individual (dominant or subordinate) to the observed firing rates in amygdala and hippocampus. In the amygdala, but not in the hippocampus, the first principal component (PC #1) of the neural responses shows significant tuning to the social status of the fixated individual. These results suggest that neurons in the primate amygdala become tuned to the social status of individuals based on observing simulated dominant-subordinate interactions.

Disclosures: S. Lee: None. **U. Rutishauser:** None. **L.J. Young:** None. **K.M. Gothard:** None.

Poster

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Program #/Poster #: PSTR096.29/GG19

Topic: G.03. Motivation

Support: P50 MH100023
R01 MH121009

Title: Videos with social content elicit saccades phase aligned to gamma and theta oscillation in the primate amygdala

Authors: H. DORMÁN[1], S. LEE[2], Z. NADASDY[3], *K. M. GOTHARD[2];
[1]Eötvös Loránd Univ., Budapest, Hungary; [2]Physiol., Univ. Arizona, Col. Med., Tucson, AZ;
[3]NeuroTexas Institute, St. David's hospital, Univ. of Texas At Austin, Austin, TX

Abstract: Eye movements can reset the phase of ongoing oscillations in multiple brain areas. We hypothesized that in the amygdala and the hippocampus the social relevance of the fixated details enhance the temporal relationship between saccade onset and the phase of ongoing oscillations. We analyzed the local field potentials (LFPs) recorded with linear arrays of 32 electrodes from the amygdala and hippocampus of two adult male monkeys. Monkeys were allowed to freely observe videos depicting simulated pairwise interactions between monkeys arranged in a virtual hierarchy of four individuals. The viewers' saccades were separated into four types based on their origin and target: from dominant to dominant (type 1-1), from dominant to subordinate (type 1-2), from subordinate to subordinate (type 2-2) and from subordinate the dominant (type 2-1). Two subclasses of socially relevant saccades were also identified: joint attention (JA) saccades, and gaze-following (GF) saccades. We asked (1) whether saccade onset is phase-aligned to low gamma (25 - 50 Hz) or theta (2 - 8 Hz) oscillations in the amygdala and hippocampus; (2) whether there are important differences between the amygdala and the hippocampus in the phase alignment of saccades to different neural oscillations; and (3) whether the magnitude/depth of phase modulation in any frequency band depends on the type of the saccade (i.e., looking from dominant to subordinate or vice versa). Fitting cosine curves to the distribution of phase angles of low gamma and theta oscillations at saccade onset, we found 94 samples (theta: 42 (9.1%), low gamma: 52 (11.2%)) in the amygdala and 47 samples (theta: 23 (6.7%), low gamma: 24 (7%)) in the hippocampus, respectively, showing significant phase-dependency of saccade onset. We found no significant difference in the depth of either gamma- or theta-phase modulation of saccade onset between the amygdala and the hippocampus. Importantly, the modulation depth was significantly higher, when the viewer monkey shifted his gaze from the subordinate to the dominant animals (Wilcoxon rank-sum test, p-value: 0.0165). Our results suggest that despite the brevity of the gamma cycle, spontaneous eye movements triggered by movie frames with social content occur at specific phases of the ongoing neuronal oscillation. The magnitude of this effect is amplified by social context, i.e., the learned dominance status of the observed individuals. We also confirm previous theta-related findings from the human amygdala and hippocampus (Staudigl et al., 2022).

Disclosures: H. Dormán: None. **S. Lee:** None. **Z. Nadasdy:** None. **K.M. Gothard:** None.

Poster

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.30/GG20

Topic: G.03. Motivation

Support: Conacyt 736014

Title: Virtual chicken's game adaptation to study social cognition with hyperscanning

Authors: *L. I. QUESADA-OLGUÍN[1], G. D. ORTIZ LAGUNES[2], J. D. ARZATE-MENA[3], Y. DEL RÍO PORTILLA[2];
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Abstract: Social cognition refers to the behavioural processes that exist in response to other individuals' behaviour within the same species and, particularly, to those higher-order cognitive processes that depend on social behaviour. Game theory has been proved to be useful in the investigation of the neural basis of social interaction, since it allows a formal definition of social situation in which the players may profit or lose by cooperating or competing (Astolfi, et al., 2010). The aim of this pilot study was to test an automated version of the Chicken's Game which was programmed and designed by our laboratory team. The Chicken's game (a variation of the Prisoner dilemma) involves two players and two possible choices: to cooperate or defect. The situation modelled is as follows: two drivers are running towards each other in a single-line street. The first to stop is called *the chicken*. However, if neither player stops, the result is a potentially fatal car crash between them. The principle of the game is that while each player prefers not to concede to the other, the outcome where neither player gives up is the worst possible one for both players. If both players cooperate, i.e. if they both stop, they have small wins (Cooperation condition). If one player cooperates and the other defects (does not stop), the cooperator has a loss and the defector has a win. If both players defect, they have a big loss (Defect condition).The aim of the game is to reach the highest possible score. This automated version of the game will be used in a further hyperscanning study. The simultaneous recording of the EEG in couples of interacting subjects will allow us to observe and model directly the neural signature of human interactions in order to understand the cerebral processes generating and generated by social cooperation or competition. In this first pilot test, we evaluated five player couples, and we were able to see that the couples that reported being the closest to each other had higher scores (the cooperated more), which is why we chose to measure the level of closeness between the participating subjects using the Inclusion of Other in the Self (IOS) Scale (Aron et al., 1992) and integrate this measure to contrast with the results obtained by the hyperscanning. There is a sample of test subjects currently being registered with EEG hyperscanning. These results will be presented at the congress.

Disclosures: L.I. Quesada-Olguín: None. **G.D. Ortiz Lagunes:** None. **J.D. Arzate-Mena:** None. **Y. del Río Portilla:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.01/HH1

Topic: G.04. Emotion

Support: P30GM145497

Title: Neonatal pain induces lasting tactile hypersensitivity mediated by neurons in the amygdala

Authors: *E. NAESS[1], E. DITOMASO[2], A. FOX[2], M. A. BURMAN[3];
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Abstract: Infants that undergo traumatic experiences early in life face an elevated risk of developing adverse mental health outcomes and altered pain thresholds later in life. One potential source of early-life trauma is the neonatal intensive care unit (NICU). While the number of infants that spend time in the NICU has increased sharply in the past decade, our understanding of the neurobiological mechanisms that predispose this patient group to altered pain thresholds remains limited. We have adopted a rodent model that mimics the NICU experience to provide better insight into this phenomenon. Male Sprague Dawley rodents were subjected to hind paw needle pricks four times per day for the first week of life followed by fear conditioning on postnatal day (PD) 24. This was followed by an assessment of fear behavior in early adolescence on PD 25 and PD26 and an assessment of the tactile withdrawal threshold using Von Frey filaments on PD 27. We have previously established that this protocol induces tactile hypersensitivity that requires both the NICU-like experience and the fear conditioning. In this study, we test the hypothesis that neurons in the amygdala are essential for the development of the conditioning-induced hypersensitivity to tactile pain following NICU-like medical trauma. Following painful neonatal manipulations, neurons in the amygdala were silenced using a chemogenetic designer receptor exclusively activated by designer drugs (DREADD) approach during fear conditioning. An initial experiment targeted neurons in the central nucleus of the amygdala that express the neuropeptide corticotrophin-releasing factor (CRF) using a combination of transgenic *Crh*-Cre rats and a Cre-dependant hM4D(Gi) DREADD expressed following successful viral vector transduction. Silencing CRF cells had a modest effect on the observed hypersensitivity. In a follow-up study, chemogenetic silencing of all neuron types in the amygdala of male rodents greatly reversed the fear-conditioning-induced hypersensitivity to tactile pain observed following early-life trauma. These findings contribute to our understanding of the neurobiological basis of altered pain thresholds associated with adverse early-life events and suggest that non-CRF-expressing neurons in the amygdala may play a critical role in this phenomenon.

Disclosures: E. Naess: None. **E. DiTomaso:** None. **A. Fox:** None. **M.A. Burman:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.02/HH2

Topic: G.04. Emotion

Support: P30GM145497
Kahn Family Foundation Summer Research Fellowship

Title: The impact of neonatal pain on the development and cellular physiology of the central nucleus of the amygdala

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Abstract: Time spent in the neonatal intensive care unit (NICU) has been shown to increase susceptibility to pain- and anxiety-disorders in later life. Using a rodent model of a typical NICU experience, our lab previously observed altered pain and anxiety responses in adolescent rats that had experienced neonatal trauma and associated this pain-vulnerability with changes to cells expressing corticotropin releasing factor (CRF) in the central nucleus of the amygdala (CeA). The CeA is comprised of a functionally heterogeneous population of GABAergic neurons that are defined by expression of various biomarkers such as CRF, somatostatin (SOM), dynorphin (DYN), protein kinase C delta (PKC-δ). These cellular populations play distinct roles in anxiety, fear, and pain, but have not been explored developmentally. Current research often fails to consider co-expression of multiple markers, including with CRF. We hypothesize that neonatal trauma alters the composition and function of biomarker-identifiable subpopulations within the CeA-CRF system, creating a pain-induced neural plasticity that primes the subjects for altered pain responses and anxiety-like behaviors in later-life. To replicate a NICU experience, neonatal rats receive a small needle prick in the hind paw four times a day, every two hours, for the first week of life. On PD 12, 24, and 48, brain tissue is collected from male and female rats that experienced neonatal pain or were left undisturbed. To assess changes in the cellular composition of the CeA, we performed fluorescent *in situ* hybridization (fISH) to visualize expression of CRF, SOM, and DYN. We find age-dependent changes in the number, biomarker-phenotype, and patterns of biomarker co-expression. To further understand these changes, acute-slice patch-clamp electrophysiology was conducted at PD 24 to assess CeA-CRF+ cell excitability and the impact of neonatal trauma. Recordings taken from transgenic rats expressing TdTomato in CRF+ neurons have revealed that CeA-CRF+ cells display at least three distinct firing patterns (e.g., regular spiking, late firing, and burst firing) that impact both membrane potential and rheobase. Furthermore, data suggest that neonatal trauma may lead to an altered rheobase and current threshold. Future analysis will examine how these changes differ in biomarker-identified subpopulations.

Disclosures: **M. Tomasch:** None. **B. Merrill:** None. **J. Zuke:** None. **M.A. Burman:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.03/HH3

Topic: G.04. Emotion

Support: NIH Grant P20GM103423
NIH Grant P30GM145497
Kahn Family Scholarship
BioMe Scholarship

Title: Epigenetic changes in DNA methylation are involved in the lasting changes in pain sensitivity following neonatal intensive care unit (NICU)-like treatment in rats

Authors: *A. J. G. FOX[1], J. ZUKE[2], M. TOMASCH[5], E. NAESS[3], A. J. KENNEDY[6], M. A. BURMAN[4];
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Abstract: Neonates that spend prolonged time in the Neonatal Intensive Care Unit (NICU) in hospitals have shown an increased susceptibility to chronic later-life pain and sensory and cognitive disorders. Our lab has adopted a procedure in which neonatal rodents are exposed to a NICU-like experience that produces altered fear- and anxiety-like behaviors, as well as lowered tactile sensory thresholds. In addition, we have observed changes in expression levels of corticotropin-releasing factor (CRF)-expressing cells in the central nucleus of the amygdala (CeA) in male, but not female, rats following our NICU manipulation. We hypothesize that the lasting changes in conditioning-induced pain sensitivity that were observed following NICU-like experiences involve changes in epigenetic regulation of crucial stress and pain-related genes including CRF. If so, then blocking or reversing these epigenetic changes using a DNA-methyltransferase inhibitor may restore normal function. Our experiments replicate the NICU experience using a neonatal rodent model in which newborn male and female rats are administered hind paw needle pricks four times a day for the first seven days of life to replicate the painful heel lancing that occurs in NICU infants. An undisturbed group will be raised alongside, but not receive the needle pricks or handling. On Postnatal Day 15 (PD), the two litters (NICU vs. undisturbed) were further split into three groups each. Within each litter, one male and one female were injected with a DNA methyltransferase inhibitor 5-Azacitidine(5-AzaC), another male and female were injected with saline, and the remaining male and female received no injection. On PD 24, all of the rodents were subjected to 3 rounds of Pavlovian fear conditioning (Davis et al. 2018). Following the fear conditioning, on PD 27, the rodents underwent Von Frey testing to determine their sensitivity to tactile stimulation given the various conditions. Animals that received the NICU-like experience demonstrated tactile hypersensitivity as previously reported. As hypothesized, the 5-AzaC injections prevented this sensitivity to

tactile stimulation in rats that received neonatal pain. In a separate set of subjects, brain tissue was collected at PD 24. The amygdala and hypothalamus were dissected out and homogenized. We then sequenced the methylome with the prediction of increases in DNA methylation at crucial stress, pain, and plasticity-related genes. Together, these data suggest that NICU exposure produces changes in the epigenetic regulation of key genes in the amygdala and hypothalamus that contribute to later-life pain sensitivity.

Disclosures: **A.J.G. Fox:** None. **J. Zuke:** None. **M. Tomasch:** None. **E. Naess:** None. **A.J. Kennedy:** None. **M.A. Burman:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

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Program #/Poster #: PSTR097.04/HH4

Topic: G.04. Emotion

Support: JSPS KAKENHI 21H02816
JSPS KAKENHI 23K08391
AMED JP23ek0610026
JSPS KAKENHI 23K16173

Title: Long-lasting mechanical sensitization at the hindlimb primed by trigeminal inflammatory pain is attenuated by analgesics affecting amygdala activities in rodents.

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Abstract: Widespread sensitization (WS) is one of the hallmark symptoms of primary chronic pain, characterized by augmented nociception in various and remote sites of the body without injury/inflammation or neuropathy. The central sensitization resulting from nociplastic changes in the brain pain networks is likely to underlie the widespread sensitization. In a study conducted by Sugimoto et al. in 2021, it was demonstrated that activating hM3Dq receptors in GABAergic neurons of the right central amygdala (CeA) leads to heightened sensitivity to mechanical stimuli in both hindlimbs. Furthermore, the activation of right CeA neurons was observed when short-lasting inflammation was induced using formalin on the lips, resulting in long-lasting sensitization in the bilateral hindlimbs. This sensitization was reduced by activating hM4Di receptors in the right CeA, indicating the crucial role of the right CeA in central sensitization. Gabapentinoids, which affect excitatory synaptic transmission in the CeA (Yamamoto et al. in 2021), such as pregabalin at a dose of 30 mg/kg (i.p.) or mirogabalin besylate at a dose of 10 mg/kg (i.p.), significantly alleviated this hindlimb sensitization even 6-10 days after the initial transient inflammation. However, celecoxib at a dose of 20 mg/kg (i.p.) did not show any

effectiveness. There was no noticeable increase in major inflammatory factors on the tenth day of inflammatory priming, despite the persistence of sensitization. Considering that alpha2delta subunits are abundantly expressed in the central/basolateral amygdala, parabrachial nucleus, and periaqueductal grey, it is likely that gabapentinoids exert their effects by modulating these brain structures, which play a role in central sensitization in nociplastic pain models.

Disclosures: M. Yajima: None. **Y. Takahashi:** None. **S. Yamamoto:** None. **H. Kawahara:** None. **F. Kato:** 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.; a recipient of a collaborative study on the effects of novel gabapentinoids with Daiichi-Sankyo Co. Ltd..

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: G.04. Emotion

Support: JSPS KAKENHI Grant Number 23K08391
Takeda Science Foundation
The Nakatomi Foundation
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Title: Systemic inflammation affects the synaptic signaling between neurons in the parabrachial nucleus and central amygdala

Authors: N. SATO, Y. K. SUGIMURA, *Y. TAKAHASHI, F. KATO;
Department of Neuroscience, Ctr. for Neurosci. of Pain, Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Pain is an unpleasant sensory-emotional experience with diverse etiology. It is very often accompanied by inflammation resulting from innate or acquired immunity, in line with the concept that pain and inflammation function together to protect the body against adverse bodily situations. However, how the neuronal and inflammatory signals influence each other remains unclear. Recent evidence points to the crucial role of plastic changes in the parabrachial nucleus (PBN) to the central amygdala (CeA) system in establishing long-lasting pain behaviors, such as widespread sensitization (Sugimoto et al, 2021; Kato et al, 2018). Interestingly, the PBN and CeA are the non-circumventricular nuclei showing the earliest activation by systemic injection of lipopolysaccharide (LPS), an activator of type 4 toll-like (TLR4) receptors in rodents (Richard et al, 2005; Sadler et al, 2017). We analyzed the PBN-CeA synaptic transmission in the brain prepared from LPS- or saline-treated mice to understand how these systems interact. We removed the brain and made slices 2 h or 24 h after injection of LPS (0.5 mg/kg, i.p.) to record postsynaptic currents elicited by optogenetic stimulation of fibers arising from the PBN. While the amplitude of postsynaptic excitatory currents (EPSC) evoked by light-stimulation of fibers

arising from PBN neurons expressing calcitonin gene-related peptide (CGRP) was not significantly different between the slices from LPS- and saline-treated mice, the disinhibition by an inverse agonist of mu-opioid receptors (MORs) was significantly larger in the LPS-treated groups. Application of DAMGO confirmed that presynaptic modulation of release probability by MORs underlies this effect, indicating that PBN neurons with MORs expression are involved in transmitting inflammatory information to the CeA. To further analyze the functional identity of these PBN-CeA transmissions in LPS-treated mice, LPS was injected into FosTRAP::A14 mice to induce channelrhodopsin expression in the PBN and tdTomato in the whole brain in the neurons priorly activated by LPS. Interestingly, the amplitude of postsynaptic inhibitory currents in the CeA neurons, presumably arising from GABAergic CeA neurons, triggered by light-stimulation of fibers from PBN neurons priorly activated by LPS was larger in the CeA neurons with prior LPS treatment. These findings indicate that systemic inflammation alters synaptic transmission in the PBN-CeA system and local CeA networks, with potential modulation by intrinsic opioid systems to regulate the association between nociception and inflammation.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Topic: G.04. Emotion

Support: NIMH Grant 1R01MH116203
SFARI Grant #388708

Title: Genetic identification of the spinothalmo-amygdaloid pain pathway.

Authors: *S. KANG, M. YE, T. OH, R. M. EVANS, S. HAN;
Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Pain is a complex sensory and emotional phenomenon triggered by various harmful stimuli. While numerous studies have investigated different regions of the peripheral and central nervous systems to unravel the mechanisms underlying pain, our understanding of the cell-type specific neural circuits from the spinal cord to the brain in the pain pathway remains limited. In this study, we provide evidence demonstrating that the calcitonin gene-related peptide (CGRP) positive neurons in the parvicellular part of the subparafascicular nucleus (SPFp) play important roles in the perception of affective-and motivational aspect of pain. Cell-type-specific anterograde/retrograde tracing analyses of CGRP populations in the SPFp revealed that they directly receive nociceptive inputs from the spinal dorsal horn, particularly the superficial layer, and project their axonal terminals to well-known pain-related brain regions, such as the amygdala and posterior insular cortex. Notably, the SPFp CGRP population exhibited increased calcium activity in response to mechanical, thermal, and inflammatory stimuli, and genetic

silencing of these populations resulted in reduced pain responses in animal models. Through investigating the role of CGRP neurons in the SPFp, we have identified a neural circuit that conveys and mediates the affective and motivational aspect of pain. Elucidating the functions of these circuits holds promise for enhancing our understanding of pain conditions and developing targeted treatments with minimized side effects.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Topic: G.04. Emotion

Support: NIH F31NS129269
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Title: The loss of sigma-2 receptor/TMEM97 prevents the development of prolonged neuropathic pain-induced depression in mice

Authors: *V. M. HONG[1,2], A. D. RADE[1], M. YAN[1], T. A. EHSAN[1], M. YOUSUF[1,2], D. J. LIEBL[3], S. F. MARTIN[4], T. J. PRICE[1,2], B. J. KOLBER[1,2];
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Abstract: The sigma-2 receptor/TMEM97 is a transmembrane protein found in the endoplasmic reticulum and plasma membrane. Previous studies developed sigma-2 receptor/TMEM97 binding ligands that show anxiolytic/antidepressant-like properties and relieve neuropathic pain in rodents. Despite medical interests, little to no affective and pain behavioral characterization has been done using transgenic mice. This knowledge gap limits the progress of sigma-2 receptor/TMEM97 as a viable therapeutic target. To address this gap, our study aims to investigate the role of sigma-2 receptor/TMEM97 in 1) modulating affective and pain behaviors at baseline and 2) regulating neuropathic pain-induced affective behaviors such as anxiety and depression. We used wild-type (WT) and global TMEM97 knockout (KO) mice (Male and female C57BL6/J, aged 8-9 weeks) and conducted a battery of affective assays: open field, light/dark preference, elevated plus maze, elevated zero maze, forced swim test, and tail suspension test. The same affective battery is performed before and after 10-to-14 weeks of neuropathic spared-nerve injury (or sham treatment) to obtain the baseline and post-injury affective behaviors, respectively. Peripheral paw mechanical sensitivity was measured to assess pain hypersensitivity developed after injury between WT and TMEM97 KO mice. The experimenter was blinded to the genotype and treatment. At baseline, our results show that TMEM97 KO mice show statistically significant reduced anxiety/depression-like behaviors in

light/dark preference and tail suspension test but not in open field, elevated plus maze, and forced swim test compared to those of WT mice. This suggests that sigma-2 receptor/TMEM97 plays a modest role in modulating anxiety and depression in naïve mice. We next performed spared nerve injury in WT and TMEM97 KO mice to assess the receptor's role in a model of neuropathic pain with comorbid anxiety/depression-like behaviors. No significant difference was observed in spared nerve injury-induced mechanical hypersensitivity between WT and TMEM97 KO mice. WT mice showed depressive behaviors induced by prolonged neuropathic pain in the forced swim assay, whereas TMEM97 KO mice did not. In the presence of nerve injury, the absence of sigma-2/TMEM97 protects against the development of neuropathic pain-induced depression. In conclusion, our findings indicate that targeting sigma-2 receptor/TMEM97 may hold promise for alleviating pain-related affective comorbidities. The results highlight the importance of further investigating sigma-2 receptor/TMEM97 as a therapeutic target for psychiatric diseases related to pain management.

Disclosures: V.M. Hong: None. **A.D. Rade:** None. **M. Yan:** None. **T.A. Ehsan:** None. **M. Yousuf:** 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.; NuvoNuro. **D.J. Liebl:** None. **S.F. Martin:** 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.; NuvoNuro. **T.J. Price:** 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.; NuvoNuro. **B.J. Kolber:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Program #/Poster #: PSTR097.08/HH8

Topic: G.04. Emotion

Support: NIH Grant R00 AT009466

Title: Chronic pain and trauma reduce pleasantness of touch, but not its inhibition of pain

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Abstract: Light stroking and deep pressure are commonly embedded in social touch interactions as well as in manual therapies, and lead to pleasant relaxation and pain relief. However, the mechanisms by which they relieve pain are poorly understood. The pleasantness of gentle stroking relies in part on activation of C-tactile (CT) afferents in hairy skin that are tuned to

gentle stroking at velocities around 1-10cm/s, while deep pressure appears to rely on A-fibers. While both forms of touch have demonstrated pain relief, their effects have not been directly compared. Furthermore, while recent studies have demonstrated reduced CT touch pleasantness in individuals with chronic pain or with trauma history, the effects of trauma or chronic pain on deep pressure pleasantness or on touch-induced pain relief have not been studied. We modified the widely studied Conditioned Pain Modulation (CPM) paradigm, in which an initial pain stimulus reduces perceived pain of a subsequent pain stimulus, to study the effect of gentle brushing and deep pressure on heat pain perception. Our preliminary findings from 28 adults (all female; ages 20-65; 10 with Fibromyalgia) demonstrate significant touch-induced pain reductions from both gentle brushing and deep pressure ($p < 0.05$), but not from tapping (control condition; $p = 0.41$). Preliminary correlation analyses demonstrate that higher levels of childhood trauma are associated with reduced pleasantness of light brushing ($N = 28$, $r = -0.48$; $p = 0.01$), deep pressure ($N = 28$, $r = -0.44$; $p = 0.02$), and also tapping ($N = 28$, $r = -0.62$; $p < 0.01$). Similarly, higher intensity of chronic pain was associated with reduced touch pleasantness (all touch conditions $p < 0.05$). Childhood trauma was associated with reduced average touch pleasantness, even after controlling for chronic pain intensity (childhood trauma beta = -0.54, $p = 0.007$). In contrast, there was no attenuation of the CPM effect associated with either chronic pain intensity or childhood trauma. These results suggest that the pleasantness versus pain relief induced by touch may rely on partially distinct mechanisms, such that reduced touch pleasantness in chronic pain does not necessarily reduce its ability to relieve pain.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Topic: G.04. Emotion

Support: Chhatrapati Shahu Maharaj National Research Fellowship for PhD work
Science and Engineering Research Board, New Delhi, India Grant CRG/2020/004971

Title: Neuropeptide S in the anterior cingulate cortex suppresses pain-related aversion via activation of GABAergic neurons

Authors: *H. M. KAWADE[1], U. P. PATIL[1], N. K. SUBHEDAR[2], D. M. KOKARE[1];
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Abstract: The role of neuropeptide S (NPS) in the sensory pain is extensively studied, however effect of NPS on affective dimension of pain and underlying mechanisms have not been clarified. The anterior cingulate cortex (ACC) is recognized as an important site for mediating

affective dimension of pain. Particularly, the GABAergic inhibitory transmission in the ACC has been emerged as a key player in the affective dimension of pain. NPS receptors are localized in the ACC and NPS-NPS receptor system is downregulated within ACC of complete Freund's adjuvant-injected rats, a model of chronic inflammatory pain and pain-related anxiety. Herein, we investigated the role of NPS in pain-induced aversion and underling mechanisms in adult male Wistar rats. Using formalin-induced conditioned place aversion model we tested the effect of NPS on pain-induced aversion. Intra-ACC NPS administration prior to intra-plantar formalin injection suppresses pain-related aversion, but not nociceptive behavior as compared to aCSF-injected control (n = 8/group). The double immuno-histochemical analysis revealed the presence of NPS receptors on GABAergic neurons in the ACC (n = 4/group). NPS administered directly in the ACC showed increase in cFOS expression in the GABAergic neurons of formalin-treated rats as compared to aCSF-control within ACC (n = 4/group). The data suggest that NPS in the ACC activates the GABAergic neurons and attenuate pain-induced aversion in formalin-treated rats.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

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Program #/Poster #: PSTR097.10/HH10

Topic: G.04. Emotion

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ATIP-AVENIR INSERM
Fondation pour la Recherche Médicale (FRM)
Région Nouvelle Aquitaine

Title: Dopaminergic regulation and electrophysiological signature of anterior insular cortex neurons in anxiety-like behaviors

Authors: *Y. COUDERC[1], G. VARDIERO[2], M. D'ALMEIDA[2], J. GJORGJIEVA[3], E. VALJENT[4], A. BEYELER[2];
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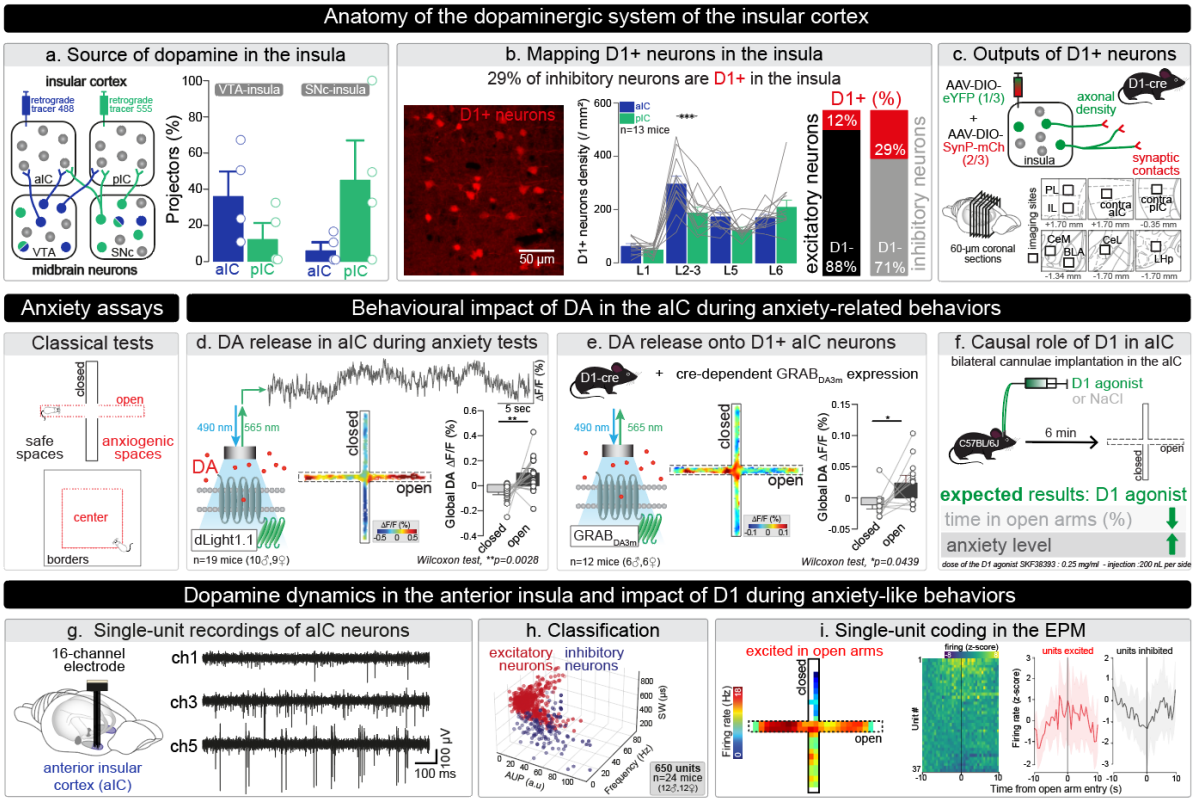
Abstract: Anxiety is an adaptive response which can become pathological. Although anxiety disorders represent the most prevalent psychiatric conditions, the underlying neurobiology remains largely unknown. Numerous studies in humans and in preclinical models revealed the implication of different neuromodulators including serotonin, norepinephrine, but also dopamine (DA)[1]. In addition, imaging studies identified that the insular cortex (or insula) and the

amygdala, are both overactivated in patients with anxiety disorders. In parallel, preclinical studies confirmed the implication of the amygdala in anxiety-like behaviors, and our lab revealed that neurons of the anterior insula are activated in anxiogenic environments and have anxiogenic properties[2]. Interestingly, activation of type 1 DA receptors (D1) within the amygdala has an anxiogenic effect in rodents. Although the D1 is also expressed in the insula, its role in the control of anxiety remains unknown.

The goal of this preclinical study is to define the impact of DA release and D1 receptors in the anterior insula (aIC), on anxiety-like behaviors.

Thus, we tested the hypothesis that DA release in the aIC promotes anxiety-like behaviors in 10 week-old male and female mice, at three levels of analysis. **1.** Anatomically, we mapped the origin of DA to the insular cortex and our preliminary results suggest that the ventral tegmental area is the major source of DA in the insula. We also identified that D1+ neurons are denser in the anterior compared to the posterior insula (aIC vs. pIC). Finally, we evidenced that D1+ insula projections mainly target amygdala nuclei and the contralateral insula.**2.** At the dopamine level, using fiber-photometry recordings, we uncovered an increase in DA release when mice are located in anxiogenic spaces, and that this DA release targets D1+ neurons.**3.** Electrophysiologically, we performed single-unit recordings of aIC neurons during anxiety assays to identify how DA modulates coding properties of aIC neurons.

References[1] de la Mora MP et al. *Prog Neurobiol*. 2010[2] Nicolas C et al. *Nature Communications*. *in press*



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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Title: Identification of a locus coeruleus-amygdala angiotensinergic circuit: Implications for anxiogenesis and stress-related disease

Authors: *Z. YU, P. J. MARVAR;
Dept. of Pharmacol. & Physiol., The George Washington Univ., Washington, DC

Abstract: Background: The brain renin-angiotensin system (RAS) mediates stress-related cardiovascular diseases, but the central mechanisms responsible for this remain unknown. Angiotensin (Ang) II and its receptors have been previously identified in the locus coeruleus (LC), a major noradrenergic nucleus of the brain that plays a critical role in modulating cardiovascular arousal and anxiety-like behaviors. The current study sought to further understand the function of Ang II and its type 1 receptor (AT_1R) in this nucleus. **Methods:** Using AT_1R-eGFP, AT_1R-Flox, and AT_1R-Cre mice combined with neuroanatomical tract-tracing, genetic deletion, chemogenetic and behavioral approaches, we examined AT_1R expressing neurons in the LC to assess their role in anxious behavior. Dual immunohistochemistry was used in AT_1R-eGFP reporter mice to characterize LC-AT_1R-$eGFP^+$ cells by looking at the colocalization of noradrenergic neuron marker tyrosine hydroxylase (TH) and GFP. Cre-inducible tracing with AT_1R-cre mice was applied for circuit anterograde analysis. *In vivo* gene deletion and chemogenetics were used for anxiety behavior testing and analysis. **Results:** Most of the AT_1R-$eGFP^+$ neurons (94%) in the LC were co-localized with TH. Anterograde virus labeling revealed that the AT_1R^+ neurons in the LC predominantly send projections to the amygdala and extended amygdala regions. Furthermore, within the amygdala, the AT_1R^+ nerve terminals were restricted to the medial division of the central amygdala (CeM) and the basomedial amygdala (BMA). Following these findings, we deleted AT_1R from LC by injecting Cre virus into AT_1R-Flox mice. The general anxiety level remained unchanged, but the restraint stress-induced anxiety was attenuated by LC AT_1R deletion. Cre-dependent inhibitory designer receptors exclusively activated by designer drug (hM4Di DREADD) with Clozapine-n-oxide (CNO) were also used to silence the AT_1R^+ neurons in the LC selectively. AT_1R^+ neuron inhibition decreased the baseline anxiety level in mice, while the restraint stress-induced anxiety behavior was unaffected. Furthermore, the acoustic startle response, which is associated with anxiety levels, was also decreased after silencing the LC AT_1R^+ neurons. **Conclusion:** These findings suggest that an angiotensinoceptive LC neuron population, projecting to the extended amygdala, positions Ang II acting on the AT_1R as a potential mediator of LC-amygdala noradrenergic activation. Future studies are needed to examine Ang II noradrenergic facilitation, a likely circuit mediating stress responses that are associated with cardiovascular disease.

Disclosures: Z. Yu: None. **P.J. Marvar:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.12/HH12

Topic: G.04. Emotion

Support: MH118237

Title: Repeated restraint stress induces sex-dependent activation of BNST and anxiety-like behavior

Authors: *R. J. MONTES[1], J. E. VANTREASE[2], J. ROSENKRANZ[2];
[1]Rosalind Franklin Univ. of Med. and Sci., Des Plaines, IL; [2]Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Anxiety disorders are among the most prevalent psychiatric disorders, with women being twice as likely as men to be diagnosed. This suggests underlying sex differences in the neural circuitry may contribute to the prevalence of anxiety disorders in females. The bed nucleus of the stria terminalis (BNST) is sexually dimorphic, stress-sensitive, and activated during anticipatory anxiety or anticipation of a threat. Prior studies show that female rodents extinguish conditioned freezing to anticipatory anxiety faster than males. However, the extent to which stress modulates anticipatory anxiety in parallel with BNST activation is unknown. Since females are more sensitive to stress and the stress hormone, corticotropin releasing factor (CRF), we hypothesized that anticipatory anxiety would facilitate greater BNST activation in stressed females compared to stressed males and control animals. To test our hypothesis, we used male and female rats exposed to repeated restraint stress (20 min/day for 7 out of 9 days) or control handling. Following treatment, rats underwent prolonged cued fear conditioning (5 random foot shocks during an 8-minute tone). In a separate context 4 days later, rats underwent extinction to the tone. Afterwards, we immunostained the BNST for c-Fos expression and CRF. There was no difference in time spent freezing during extinction, therefore, we also quantified active behaviors (e.g., darting, scanning, etc.). We found significant interactions between stress and sex with stress females rearing (*p=0.0234) and scanning (*p=0.0272) less than control females, whereas stressed males reared and scanned more than controls during the tone. Preliminary data further suggests that these stress-induced sex differences on anxiety-like behaviors may be related to c-Fos expression in the BNST. We found increased c-Fos expression in the BNST of stressed rats compared to controls (p=0.0544). Additionally, we found BNST CRF expression was higher in females (*p=0.0324) and affected by stress in a sex-dependent manner (*p=0.0452) with CRF expression increased in stressed females but decreased in stressed males. Together, these studies show how stress influences anxiety-like behaviors in a sex-dependent fashion, possibly through differences in activation of the BNST.

Disclosures: R.J. Montes: None. **J.E. Vantrease:** None. **J. Rosenkranz:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.13/HH13

Topic: G.04. Emotion

Support: National Natural Science Foundation of China

Title: Stress affects the physiological states through activating orexin neurons in mice

Authors: *Z.-K. DING, X. YU;
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Abstract: The orexins, or hypocretins, are a couple of neuropeptides discovered in 1998, the efferent fibers of orexin neurons widely innervate the whole brain and control many crucial physiological states, such as blood pressure, breathing rate, and sleep architectures. Stress induces elevated blood pressure, accelerated breathing rate, and altered sleep patterns. However, the mechanisms remain exclusive. As orexin neurons strongly respond to stressors in mice, we assumed that orexin system may causally link negative emotion and physiological states. Then we started investigating this hypothesis by measuring the activity of orexin neurons responding to stress, and if genetically manipulate the function of orexins/hypocretins influences physiological state linked to emotion in mice. Here, we commanded various technologies such as optogenetics, chemogenetics, fiber photometry, tail vein blood pressure measurement, whole-body plethysmograph and *in vivo* electrophysiological recording that demonstrated the stressors activate orexins/hypocretins cells causing an increased extracellular orexin concentration in the LH measured by a genetically encoded sensor. In addition, we identified a novel circuit linking stress and physiological states, e.g., elevated blood pressure, accelerated breathing rate, and altered sleep patterns through the orexins/hypocretins element, providing a new perspective how negative emotion (stress) affects physiological states in our body.

Disclosures: Z. Ding: A. Employment/Salary (full or part-time):; Center for Excellence in Brain Science and Intelligence Technology. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Center for Excellence in Brain Science and Intelligence Technology. **X. Yu:** A. Employment/Salary (full or part-time):; Center for Excellence in Brain Science and Intelligence Technology. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Center for Excellence in Brain Science and Intelligence Technology.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.14/HH14

Topic: G.04. Emotion

Title: Gabaergic neurons in the bed nuclei of stria terminalis to ventral hippocampus mediate anxiodepression-like behaviors induced by trigeminal neuropathic pain

Authors: *Z. ZHANG, T.-T. LIU, Y.-Q. ZHANG;
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Abstract: Abstract: Objective Trigeminal neuropathic pain (TN) is one of the most common chronic pain in the world. Patients suffering from long-term pain are often accompanied by mental diseases such as anxiety and depression. However, the exact neural mechanism of TN comorbidity is still unclear. In our previous study, the bed nuclei of stria terminals (BNST) as the relay station of emotional regulation in the central nervous system could be activated by TN. **Methods** Chronic constriction injury of infraorbital nerve (CION) was used to construct a model of trigeminal neuropathic pain. Using virus tracing, electrophysiology, fluorescence in situ hybridization, optogenetic manipulation, chemogenetic manipulation, and ethology, we systematically investigated the roles of the projection from BNST to vHPC in regulating chronic pain and its anxiodepressive consequences. **Results** (1) Silencing of GABAergic and corticotropin-releasing factor producing (CRF) neurons in the BNST attenuates mechanical allodynia and anxiodepressive-like behaviors caused by TN. (2) BNST GABAergic neurons projecting to vHPC selectively and inhibiting of the pathway relieved both sensory and emotional aspects induced by TN. **Conclusion** BNST GABAergic neurons, exclusively CRF neurons, which could offer therapeutic targets for TN as well as any other kinds of neuropathic pains.

Disclosures: Z. Zhang: None. **T. Liu:** None. **Y. Zhang:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.15/HH16

Topic: G.04. Emotion

Support: NIH Grant NS122181
Kavli Distinguished Graduate Student Fellowship

Title: Investing the Identity and Function of mWAKE^{+} neurons in the Central Amygdala

Authors: *J. XIONG[1], B. J. BELL[2], M. N. WU[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Neurol., Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: Animals exhibit 24-hour daily rhythms regulated by clock-related molecules. However, our understanding of how circadian rhythms influence context-dependent behaviors, including fear learning, is currently limited. In my project, I aim to investigate the role of the clock-output molecule mWAKE in the circadian regulation of fear learning. Specifically, I manipulate the mWAKE-positive cells in the central amygdala (CeA^{mWAKE} cells) to uncover their involvement in fear learning. By utilizing different mouse transgenic mouse lines, I have successfully uncovered the genetic identity and the projection pattern of those cells. Additionally, my behavioral data has demonstrated the regulatory role of CeA^{mWAKE} cells in fear learning.

Disclosures: J. Xiong: None. **B.J. Bell:** None. **M.N. Wu:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.16/HH17

Topic: G.04. Emotion

Title: Esr1+ hypothalamic-habenula neurons shape aversive states.

Authors: *D. CALVIGIONI[1,2], J. FUZIK[2], P. F. LE MERRE[2], M. SLASHCHEVA[2], F. JUNG[2], C. ORTIZ[2], A. LENTINI[2], V. CSILLAG[2], M. GRAZIANO[2], I. NIKOLAKOPOULOU[2], M. WEGLAGE[2], I. LAZARIDIS[2], H. KIM[2], I. LENZI[2], H. PARK[2], B. REINIUS[2], M. CARLEN[2], K. MELETIS[2];
[1]Neurosci., [2]Karolinska Institutet, Stockholm, Sweden

Abstract: Excitatory projections from the lateral hypothalamic area (LHA) to the lateral habenula (LHb) drive aversive responses. We used Patch-seq guided multimodal classification to define the structural and functional heterogeneity of the LHA-LHb pathway. Our classification identified six glutamatergic neuron types with unique electrophysiological properties, molecular profiles, and projection patterns. We found that genetically-defined LHA-LHb neurons signal distinct aspects of emotional or naturalistic behaviors: Esr1+ LHA-LHb neurons induce aversion, whereas Npy+ LHA-LHb neurons control rearing behavior. Repeated optogenetic drive of Esr1+ LHA-LHb neurons induces a behaviorally persistent aversive state, and large-scale recordings showed a region-specific neural representation of the aversive signals in the prelimbic region of the prefrontal cortex. We further found that exposure to unpredictable mild shocks induced a sex-specific sensitivity to develop a stress state in female mice, which was associated with a specific shift in the intrinsic properties of bursting-type Esr1+ LHA-LHb neurons. In summary,

we describe the diversity of LHA-LHb neuron types, and provide evidence for the role of Esr1+ neurons in aversion and sexually dimorphic stress sensitivity.

Disclosures: D. Calvigioni: None. **J. Fuzik:** None. **P.F. Le Merre:** None. **M. Slashcheva:** None. **F. Jung:** None. **C. Ortiz:** None. **A. Lentini:** None. **V. Csillag:** None. **M. Graziano:** None. **I. Nikolakopoulou:** None. **M. Weglage:** None. **I. Lazaridis:** None. **H. Kim:** None. **I. Lenzi:** None. **H. Park:** None. **B. Reinius:** None. **M. Carlen:** None. **K. Meletis:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.17/HH18

Topic: G.04. Emotion

Title: Voluntary oral consumption of cannabidiol does not reduce anxiety-like behaviors in rats

Authors: *S. R. BOND, J. NERZ, M. LASATER, K. J. LEISING;
Psychology, Texas Christian Univ., Fort Worth, TX

Abstract: Cannabidiol (CBD) is one of many cannabinoids derived from the *Cannabis sativa* plant. There is some evidence that it reduces anxiety (i.e., acts as an anxiolytic) at certain doses. In rodents, it has been found that 10 mg/kg intraperitoneal (i.p.) injections of CBD result in anxiolytic effects in the elevated plus maze (EPM) (Blessing et al., 2015). In the current set of experiments, we explored the effectiveness of voluntary oral CBD consumption to reduce anxiety-like behaviors in rats. Anxiety-like behaviors were assessed using separate 5-min EPM and elevated open field (OF) tests. CBD was expected to increase the percentage of time rats spent in the open arms of the EPM and in the center of the OF. In Experiment 1, rats were given either nonpharmaceutical grade CBD (20 mg/kg) dissolved in MCT coconut oil or coconut oil alone (20 mg/kg) (n = 9 rats per group). The solutions were dripped over standard rat chow, which was ground into a powder to facilitate absorption of the oils. Once daily for two days, rats were given 30-min to consume the oils and tested 2-hrs later on the EPM or OF. Experiment 2 was conducted in the same manner, but with chronic delivery (12 days) of CBD (20 mg/kg) dissolved in MCT coconut oil in the experimental group and distilled water for the control group (.25 ml) (n = 8 rats per group). Rats were tested on days 13 and 14. This same procedure was used in Experiment 3, except pharmaceutical grade CBD (20 mg/kg) was used and dissolved in extra virgin olive oil, the control group received extra virgin olive oil alone (20 mg/kg) (n = 11 rats per group), and administration was across 16 days with testing occurring on days 17 and 18. In Experiment 2, the CBD group spent more time in the center compared to the control group on the OF, but there were no other differences between groups in any experiment. The EPM is a common assessment of anxiety-like behaviors in rodents, however, we found no group differences using this test. Future testing will include different concentrations, oils, controls, and different tests of anxiety to further explore the effectiveness of CBD as an anxiolytic with voluntary oral consumption.

Disclosures: **S.R. Bond:** None. **J. Nerz:** None. **M. Lasater:** None. **K.J. Leising:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.18/HH19

Topic: G.04. Emotion

Support: NS119847

Title: Suppression of the paratenial nucleus of the midline thalamus produces anxiolysis as assessed with the elevated plus maze

Authors: *A. K. P. ROJAS, R. P. VERTES;
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Abstract: The midline nuclei of the thalamus consist of the paratenial (PT) and paraventricular (PV) nuclei, dorsally, and the reuniens and rhomboid nuclei, ventrally. The functional properties PV have been extensively investigated showing a PV involvement in appetitive and aversive motivational states. By contrast, little is known regarding the functional characteristics of PT. We previously examined the efferent projections of PT and PV (Vertes and Hoover, 2008) and showed, with some differences, that both nuclei distributed to several common sites, characterized as “affective-associated” structures of the forebrain. However, afferent projections to PT and PV differ suggesting that PT and PV may participate in dissociable roles to emotion, cognition, and motivation. We sought to examine the role of PT in affective behavior using the elevated plus maze (EPM). To our knowledge, this is the first behavioral examination of the functional properties of PT. Specifically, we examined the effects of suppressing PT with muscimol, compared to vehicle controls on performance on the EPM. Our results show that rats infused with the muscimol spent significantly more time in the open arms and less time in the closed arms of the maze, indicating that suppression of the paratenial nucleus has an anxiolytic effect on behavior.

Disclosures: **A.K.P. Rojas:** None. **R.P. Vertes:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

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Topic: G.04. Emotion

Support: Start-up funds from Johns Hopkins University (SPM and HA)

Title: Characterizing anxiety selectivity of individual neurons: Methodological considerations

Authors: *H. HUANG[1], G. SHAH[2], H. ADWANIKAR[3], S. P. MYSORE[2];
[1]Johns Hopkins Univ. Undergraduate Neurosci. Program, Baltimore, MD; [2]Dept. of Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [3]John Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: A common approach for investigating the neural encoding of anxiety-like states in rodent experiments involves the assessment of the 'selectivity' of individual neurons for high- versus low-anxiety zones as the animals navigate a behavioral environment such as an elevated zero maze (EZM). This assessment is typically done by computing a selectivity index for each neuron that quantifies, in a statistically rigorous manner, whether and how well the neuron's activity differentially encodes the two zones. However, especially when neural activity is measured using calcium imaging, choices in quantifying calcium dynamics as well as in the analytical and statistical procedures for estimating the selectivity index may affect the anxiety selectivity label assigned to each neuron. Here, using endoscopically imaged calcium dynamics of neurons in the mouse medial prefrontal cortex (nVoke, Inscopix, Inc), we examined systematically the effect of various choices in the processing and quantifying neural calcium activity, as well as in the analytical and statistical strategies used for calculating the selectivity index, on the classification of neurons as open arm (high anxiety zone) selective, closed arm (high anxiety zone) selective, or non-selective cells. We found that using discrete calcium events, events convolved with a 2s calcium-transient filter, or events convolved with a 4s filter, did not impact significantly the anxiety selectivity label of individual mPFC neurons. Neither did temporal binning of neural data into 50 ms bins (frame rate of the miniscope), 0.5s bins, or 1s bins. However, details of the implementation of the permutation testing procedures used for assessing the statistical significance of selectivity index had a sizeable impact on the selectivity label of the neuron. Specifically, the choice between 'randperm' and 'circshift' approaches to 'shuffle' the neural data, as well as the specific sequence of steps during the shuffling procedure affected the selectivity label greatly. Using arguments of consistency as well as neural plausibility, we provide recommendations for the preferred choices of each of these (and a few other) parameters for reliable assessment of the anxiety selectivity of individual neurons. These results provide a useful foundation for future studies investigating the neural encoding of anxiety-like states using calcium imaging.

Disclosures: H. Huang: None. **G. Shah:** None. **H. Adwanikar:** None. **S.P. Mysore:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

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Topic: G.04. Emotion

Support: JSPS KAKENHI Grant Number JP23H04370
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AMED-CREST under Grant Number 21gm1510003.

Title: Neuronal representation of emotion in the monkey parabrachial nucleus

Authors: *M. YASUDA, K. NAKAMURA;
Dept. of Physiol., Kansai Med. Univ., Hirakata, Japan

Abstract: Emotional experiences are accompanied by changes in the internal state of the body. It has long been debated whether the sensory input from inside the body contributes to the formation of the emotional experience itself. This view has been supported by recent human imaging studies which show the convergent neuronal representation of bodily sensations and emotions. However, the detailed neuronal mechanism for integrating these signals is still elusive. Afferent sensory signals from inside the body, especially visceral sensations, are sent primarily through the vagus nerve to the nucleus of the solitary tract in the medulla, which in turn reaches the parabrachial nucleus (PBN) in the upper pons. The PBN also receives other sensory inputs such as taste, pain, and heat, and also receives direct descending input from the limbic brain structure, suggesting the convergence of the body's internal sensory and emotional signals. However, the neuronal representation of emotion in PBN remains largely unexplored. We thus asked whether the activity of individual neurons in PBN would be modulated by the monkey's emotional state, and would be interacted with the bodily signal, heartbeat. To answer this question, we recorded the single neuronal activity in the PBN of a male macaque monkey *(Macaca fascicularis)*, and measured its autonomic activity (heartbeat and pupil diameter) with emotional change. First, we localized the PBN which surrounds the superior cerebellar peduncle in the upper pons. Consistent with the previous studies, we confirmed selective neural responses to different taste stimuli: juice, water, and salty water. Second, monkeys were conditioned in a Pavlovian procedure with two distinct contexts: an appetitive block where a reward was available; and an aversive one where an air puff was delivered, associated with different visual CSs. The analysis of pupil diameter and heart rate variability supported the modulation of the monkey's emotions. We found many PBN neurons exhibiting emotional context-dependent responses. Among 80 PBN task-responsive neurons, 28 differentiated appetitive and aversive contexts during CS presentation, suggesting the representation of emotional association. Third, some PBN neurons' activities were synchronized with the heartbeats, suggesting cardiovascular input to the PBN. Moreover, 6 out of 24 neurons' activity in Pavlovian conditioning was influenced by the synchrony between heart rate and task events. Such overlapping representation of body and emotion suggests that sensory signals of the internal body may be involved in the processing of emotional information in PBN.

Disclosures: **M. Yasuda:** None. **K. Nakamura:** None.

Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

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Program #/Poster #: PSTR097.21/HH22

Topic: G.04. Emotion

Support: 1R56MH115681-01

Title: Interoception biases decision-making on an approach-avoidance conflict task.

Authors: *M. A. CARDENAS[1], T. M. CHAMP[2], N. Y. SOTELO[2], R. L. PHONG[2], T. W. VANDERAH[3], A. J. FUGLEVAND[2], K. M. GOTHARD[2];
[2]Dept. of Physiol., [3]Dept. of Pharmacol., [1]Univ. of Arizona, Tucson, AZ

Abstract: Real-life decision-making often relies on the evaluation of multiple conflicting factors. In such cases, choices reflect the tradeoff between the motivation to avoid aversive stimuli and the motivation to approach appetitive stimuli. The weight an organism assigns to costs and benefits can be biased by internal and external factors. For example, anxiety, as an internal state focused on negative outcomes, biases behaviors toward avoidance (Kirlic et al., 2017). Khalsa and Feinstein (2018) proposed that a somatic prediction error, which arises from a misinterpretation of interoceptive signals, can lead to anxiety. We hypothesized, therefore, that artificially inducing peripheral autonomic states, normally associated with anxiety, will enhance avoidant choices in an approach-avoidance conflict task. To test this hypothesis, we administered a parasympatholytic drug that does not cross the blood brain barrier (glycopyrrolate). The resulting sympathetic-parasympathetic imbalance was expected to resemble the somatic expression of anxiety signaled to the brain through interoceptive afferents. On average, glycopyrrolate injection increased heart rate by 17 beats per minute compared to saline injection in 3 rhesus macaques. Our approach-voidance conflict task offered the monkeys two choices: (1) endure a hot but non-painful stimulus on their skin in exchange for a steady flow of fruit juice, or (2) turn off the heat, forgoing the juice reward. The heat stimulus (48°C) was delivered by a Medoc TSA-2 thermode attached to a shaved region of their arm. While the heat remained on (maximum 20 s per trial), monkeys received juice at a rate of 1 drop per second. Throughout the presentation of the heat stimulus, subjects could activate a button that turned off both the heat and the juice delivery. The latency to deactivate the thermode served as a measure of the animal's tolerance to the heat stimulus in exchange for receiving the juice reward. In control trials, the thermode was set to 35°C (which feels neutral against the skin). Preliminary results in one animal support the hypothesis that decreased peripheral parasympathetic tone (as indexed by increased heart rate) reduces heat tolerance. Under glycopyrrolate treatment, the average time to turn off the 48°C heat was 2.1s earlier than in saline controls (Wilcoxon rank-sum test, $p < .001$). Glycopyrrolate had no effect on the behavior during trials when the thermode set to 35°C (Wilcoxon rank-sum test, $p = .6912$). These results indicate that bodily states, communicated to the brain through interoceptive afferents, can bias decision-making on an approach-avoidance conflict task.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.22/HH23

Topic: G.04. Emotion

Support: ERC-2017-STG

Title: Interoceptive signals drive cellular and intracellular dynamics of insular neurons during emotions

Authors: *M. MALEZIEUX, J. YEONGSEOK, E. CHO, A. RESSLE, B. SCHMID, N. GOGOLLA;
Emotion Res. Dept., Max Planck Inst. of Psychiatry, München, Germany

Abstract: Insular cortex (InsCtx) is involved in the processing of emotion states in both humans and mice. Recent work has demonstrated that the posterior InsCtx acutely responds to diverse emotion-related stimuli, and processes sustained emotion and homeostatic states such as anxiety, hunger or thirst (Gehrlach et al., 2019, Klein et al., 2021, Livneh et al., 2020). Furthermore, InsCtx is important for cardioceptive processing. For example, its neurons increase activity upon heart-rate increase (Hsueh et al., 2023), and perturbing heart-to-brain communication impedes fear extinction, a process dependent on InsCtx activity (Klein et al. 2021). Thus, InsCtx processes a wide range of emotion-related external and internal inputs, and consequently generates optimal output essential for the emergence of emotion states. **Understanding mechanistically how InsCtx single-cell and neuronal population activity is modulated by emotion-relevant signals is crucial to gain better insights into how the InsCtx contributes to emotion states processing.** Here, we characterized the membrane potential dynamics of single InsCtx neurons as well as InsCtx neuronal population activity during aversive and positive emotion states. To this end, we performed whole-cell patch-clamp and silicone probe recordings in awake head-fixed mice during fear recall and appetitive conditioning. To characterize the behavioral and physiological responses associated with these distinct emotion states, we recorded and analyzed heart-rate fluctuations, pupil diameter, whisker movement, facial expressions and locomotor behavior. We found that InsCtx neurons encode for emotion states at the single-cell and population levels, with signatures of valence encoding. Furthermore, InsCtx activity does not merely reflect arousal changes, as two high-arousal states, locomotion and freezing, induce opposite changes in InsCtx activity. Additionally, InsCtx activity tightly correlates with heart-rate fluctuations. This correlation is heightened during emotion states, where heart-rate fluctuations are strongly represented by InsCtx neurons, more so than arousal changes or locomotion. In summary, our findings show that single-neuron and population activity in InsCtx are strongly influenced by interoceptive signals and may thus be essential to accurately represents distinct emotional states of opposite valences.

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Poster

PSTR097. Integrative Emotion Circuitry: Pain, Anxiety, Interoception

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Title: Idling neuronal dynamics underlie internal state and emotional memory bias

Authors: *S. UM, M. HANAFY, M. NOMOTO, R. OKUBO-SUZUKI, K. CHOKO, H. ASAI, A. SUZUKI, A. CHOUCRY, K. INOKUCHI;
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Abstract: Cognitive distortion including overgeneralization, repeated negative memory replay and self-reflection has been one of the key common features in mood disorders which leads to a frequent relapse that makes drug treatment less effective in the long run. Despite the proposed theory and emerging hints of higher-order processing of emotion, neuronal mechanism of how cognitive bias is generated and processed is still not fully understood. We hypothesized that mood may bias specific neural activity in the memory network during idling/offline state to selectively reactivate unwanted emotional memory to drive such perceptual bias of emotion at the cognitive level. Here we established a simple behavioral paradigm to test mood-induced emotional memory bias and we found that negative mood induction by repeated social defeat stress enhances emotional perception of the past emotional memory and upcoming salient event in the future. We performed chemogenetic inhibition of negative experience-specific ensemble to prove the reactivation of past emotional episode and chronic freely movable 1P Ca^{2+} imaging to identify specific neuronal representations which likely reflect the internal state of emotional episodes and displays mood-schema-like activity when mice experience new aversive situations. Surprisingly, these neuronal populations reflecting emotional episode strongly reactivate when mice are resting and sleeping after experiencing a new salient event. Finally, negative mood drives offline co-activation of two emotional memory-related representations which suggests subconscious interaction of two separate emotional events and closed-loop optogenetic inhibition of the hippocampal negative experience-specific ensemble during offline period prevent such an emotional bias in the memory. Together, we provide a new conceptual insight of how mood generates specific neuronal representation in memory network to reflect an internal state of memories and offline dynamic of these populations may underlie overgeneralization to internally determine the emotional saliency of the future event.

Disclosures: S. Um: None. **M. Hanafy:** None. **M. Nomoto:** None. **R. Okubo-Suzuki:** None. **K. Choko:** None. **H. Asai:** None. **A. Suzuki:** None. **A. Choucry:** None. **K. Inokuchi:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.01/HH25

Topic: G.05. Mood Disorders

Support: NIMH R00MH102355

Title: Striatal Subregions Differentially Predict Approach and Avoidance Following Acute Stress in Healthy Controls and Patients with Major Depression

Authors: *M. MIGÓ[1], J. A. COOPER[2], P. A. KRAGEL[1], M. T. TREADWAY[1];
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Abstract: The Affective Modes hypothesis posits that brain regions involved in valence processing may switch their affective function depending on the dynamics of the environment. In particular, prior rodent studies have found that striatal areas such as regions of the anterior caudate and the nucleus accumbens (NAcc) may switch their roles to support aversive behaviors following exposure to environmental stressors. Here, we sought to translate this phenomenon to healthy human participants, and test whether an acute stressor alters the representation of valence (i.e., responses to reward and loss cues) in the caudate and NAcc. Further, we sought to compare these changes to a sample of individuals with current Major Depressive Disorder (MDD), a common psychiatric disorder frequently precipitated by stress exposure. Two groups of healthy controls (n=25) completed a reinforcement learning (RL) task during an fMRI scan before and after an acute stress challenge (ASC) or a no-stress control (NSC). The RL task required participants to learn which stimuli were probabilistically associated with wins and losses. A PLS classifier and 5-fold cross-validation were used to test, at cue, whether approach-win and avoid-loss trials displayed uniquely different patterns of activation, compared to neutral trials, in NAcc and caudate. Prior to classification, resting state fMRI data was used to hyperalign activity in both ROIs. At baseline, we found that both the caudate (AUC = .67, p = .008) and the NAcc (AUC = .62, p = .04) were able to discriminate approach-win and neutral trials, but not avoid-loss and neutral trials. Next, we computed changes in neural activity before and after the ASC and NSC conditions and classified group membership between HC groups. NAcc was able to distinguish the presence/absence of an acute stressor (AUC = .65, p < .001), but only during approach-win trials. Conversely, the caudate classified stress/no-stress (AUC = .65, p < .001), but only during the avoid-loss trials. In a final set of analyses, we examined a third sample (n=25) of unmedicated patients with current MDD, and used an additional classifier to determine whether neural activity following acute stress belonged to individuals with MDD or healthy controls. We found that activity in the caudate–but not NAcc– was able to classify the presence of an MDD diagnosis ($AUC_{caudate}$ = .67, p < .001; AUC_{NAcc} = .42, p = .99) during the avoid-loss trials. Consistent with the affective modes hypothesis, this work suggests that appetitive and aversive cues are distinctly encoded within the anterior caudate and NAcc, and that this encoding is impacted by exposure to acute stress and stress-linked psychopathology.

Disclosures: **M. Migó:** None. **J.A. Cooper:** None. **P.A. Kragel:** None. **M.T. Treadway:** F. Consulting Fees (e.g., advisory boards); Neumora, Boehringer Ingelheim.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.02/HH26

Topic: G.08. Other Psychiatric Disorders

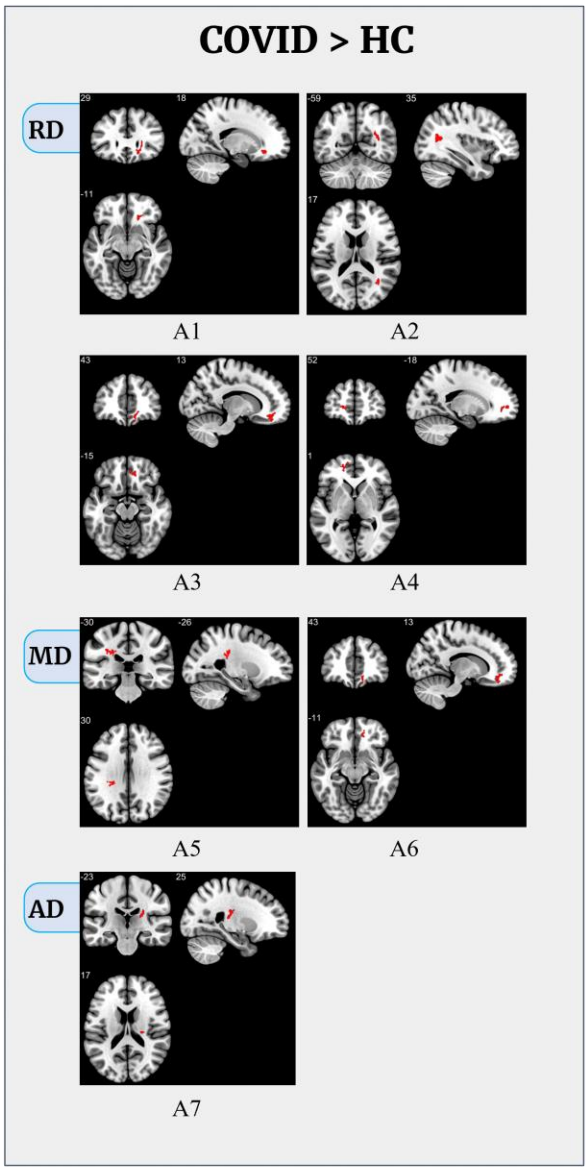
Support: The work is supported by MeitY (Government of India) under grant 4(16)/2019-ITEA
Cadence Chair Professor fund awarded to Prof. Tapan Kumar Gandhi.
Prime Minister Reseach Fellowship awarded to Sapna S Mishra

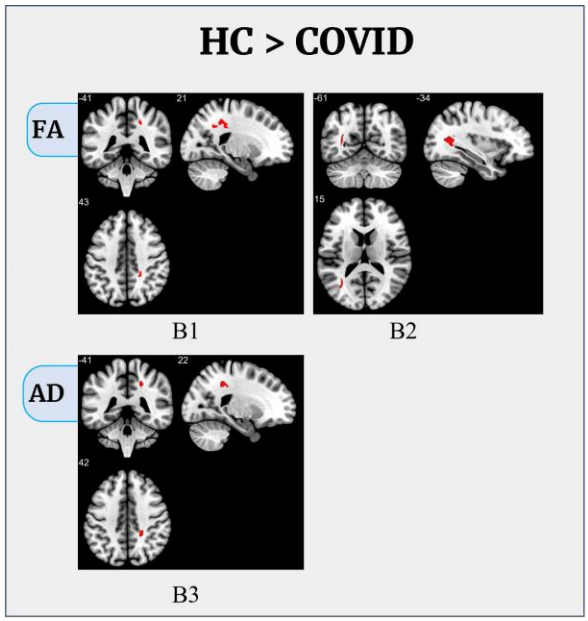
Title: Microstructural Brain Abnormalities in COVID Recovered Patients: A Voxel Based Analysis of Diffusion Tensor Imaging

Authors: *S. S. MISHRA[1], T. K. GANDHI[1], B. B. BISWAL[2];
[1]Indian Inst. of Technol. Delhi, New Delhi, India; [2]New Jersey Inst. of Technol., Newark, NJ

Abstract: An increasing number of COVID recovered patients (CRPs) are experiencing post-COVID symptoms like brain fog, memory loss, fatigue, and more. To investigate the neurological substrates of COVID-19, we conducted a cross-sectional study wherein we used Diffusion MRI (dMRI) to scan 45 CRPs (15F, 34.95 ± 11.46 years) and 30 Healthy Controls (HCs) (8F, 34.67 ± 9.5 years). Microstructural properties of white matter were studied by extracting fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) from the dMRI.
Preprocessing of dMRI was performed by first denoising, then removing the warping and Gibbs' ringing artifacts. Given we had only one phase encoding direction, the susceptibility distortions in the opposite direction were estimated using the Synb0-DISCO algorithm. The volumes were masked and corrected for susceptibility distortions using the FSL's TOPUP tool. Finally, Eddy current and motion correction was done using FSL. Diffusion tensor reconstruction was performed using Freesurfer, and the FA, MD, AD, and RD maps were generated from derived eigenvalues. The maps were masked with white matter parcellation masks to eliminate spurious values. Finally, they were registered to the standard MNI space using FSL's TBSS tool. The registered maps from both groups were compared in SPM using a two-sample *t*-test for the contrasts COVID > HC and HC > COVID with $p_{unc}<0.01$, followed by multiple comparison correction for $p_{FWE}<0.05$.
Regions belonging to forceps minor, uncinate fasciculus, and the longitudinal fasciculus showed significantly increased RD in the CRPs suggesting microstructural damage or demyelination. Cluster in corticospinal tract showed raised MD and AD in CRPs indicating possible axonal injury. The CRPs also exhibited significantly low FA in the middle longitudinal fasciculus signaling demyelination or injury in these tracts. Hence, structural abnormalities were observed

in the orbitofrontal cortex and parietal regions linking the changes to behavioral symptoms like attention deficit, fatigue, and memory loss.





Cluster	Peak t-score	Location
A1	4.6	Right Uncinate Fasciculus
A2	4.22	Right Middle Longitudinal Fasciculus
A3	4.09	Right Forceps Minor
A4	3.95	Left Forceps Minor
A5	4.55	Left Corticospinal Tract
A6	4.13	Right Forceps Minor
A7	4.12	Right Corticospinal Tract
B1	4.1	Right Middle Longitudinal Fasciculus
B2	4.38	Left Middle Longitudinal Fasciculus
B3	4.21	Right Superior Longitudinal Fasciculus

Figure 1. Results of the voxel-based analysis on diffusion tensor imaging. Clusters obtained for different diffusion measures for the two contrasts reveal microstructural changes in the post-COVID brain. The table in the bottom right provides information about the cluster locations. Keys: FA: Fractional Anisotropy, MD: Mean Diffusivity, RD: Radial Diffusivity, AD: Axial Diffusivity.

Disclosures: **S.S. Mishra:** None. **T.K. Gandhi:** None. **B.B. Biswal:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.03/HH27

Topic: G.05. Mood Disorders

Title: Amygdala reactivity in depression: false positives, states and traits

Authors: Y. HAO[1], C. XU[2], H. KWEON[3], ***M. J. FARAH**[4];
[1]Neurosci., Mount Sinai Sch. of Med., New York City, NY; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Vrjie Univ., Amsterdam, Netherlands; [4]Univ. Pennsylvania, Philadelphia, PA

Abstract: Background: Many studies have found heightened amygdala reactivity to the sight of negative facial expressions of emotion in depression. This has been interpreted as indicating a special sensitivity or attentional bias to negative affect, and thus a contributing cause of depression. However, the robustness of this finding has been questioned following meta-analysis (eg, Lai, 2014, *J Neuropsych Clin Neurosci*) and a recent test using data from the UK Biobank, the largest sample to date (n=28,638). This latter study showed no association between participants' amygdala reactivity and reported level of depression on the day of scanning (Tamm et al, 2022, *Am J of Psych*). **Question**: Rather than marking the state of depression, as assumed by many previous studies, might heightened amygdala reactivity mark vulnerability to depression? **Method**: We analyzed data from the UK biobank (ages 44-82) excluding those with morbid obesity, neurological conditions, heavy alcohol use, and those lacking MRI or Depression Status data, yielding n=6,603. Twin studies and GWAS indicate that the phenotype most associated with genetic depression vulnerability is Severe Recurrent Depression (SRD) (Flint, 2023, *Mol Psych*). Other depression phenotypes tend to be less heritable and share more genes with other psychopathologies. We used the Biobank's Depression Status measure (Field 20126) from study outset to identify participants with SRD. Using the same UKB measure of amygdala reactivity as Tamm, we compared groups with SRD and no depression history, covarying (as Tamm did) gender, age, Townsend Deprivation Index and college completion or not. **Results:** UK Biobank participants with histories of SRD (consistent with depression vulnerability, n=389), showed elevated amygdala reactivity compared to those who were never depressed (n=4,869). This was true in a univariate analysis $\beta = .14$, $p=0.009$ and with covariates $\beta=.13$, $p=0.011$. It was also true when we relaxed our exclusionary criteria to achieve equivalence with Tamm et al's sample, with n=487 and n=5,641 respectively, yielding $\beta=.11$, $p=0.017$ for univariate and $\beta=.10$, $p=0.042$ with covariates. **Conclusions**: It is premature to conclude that amygdala reactivity is unrelated to the pathophysiology or symptomatology of depression. Depression vulnerability, as indexed by history of severe recurrent depression, is accompanied by significantly increased amygdala reactivity to negative emotional faces. This is consistent with the idea that increased sensitivity or bias toward negative emotional stimuli is a diathesis for depression, or at least part of the neural phenotype of depression vulnerability.

Disclosures: Y. Hao: None. **C. Xu:** None. **H. Kweon:** None. **M.J. Farah:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.04/HH28

Topic: H.01. Attention

Title: Test anxiety without bias to threat : attentional control disruption during reorientation

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Abstract: Anxiety is typically associated with an attentional bias (AB) towards threat. However, the AB effect is known to be modified by a variety of factors and may even be reversed (i.e., an AB *away* from threat). Test anxiety, although common, is poorly characterized and it is unknown if an AB towards threat exists in this population. The purpose of this experiment was to determine if test anxiety is associated with an AB towards threat as well as identify the attentional mechanism(s) that cause the AB in test anxiety. Twenty-five students with test anxiety (TA) and twenty-nine students without test anxiety (CNTRL) (as determined by a computerized task developed and validated in our lab) completed a dot-probe task (DPT) while 9-lead electroencephalography (EEG) was recorded. The DPT consisted of 50 trials each of neutral-neutral word pairs, generally threatening word (GT)-neutral pairs, and test-specific threatening word (TST)-neutral pairs. Following a 1-second presentation of the word pair, one word was replaced with a dot; the participant indicated the location of the dot using the left or right arrow key. TA had faster reaction times than CNTRL on all trial types, but neither CNTRL nor TA had an AB towards GT or TST (measured as the difference between threat-probe discordant and threat-probe concordant trials). However, CNTRL had a significantly faster reaction time on trials containing threat (TST or GT) compared to neutral-only trials, an effect not seen in TA. Event-related potentials measured from posterior, central, and frontal sites all showed that the late portion of the P300 wave was elevated in TA on discordant TST trials (but not concordant trials, neutral-only trials, or trials containing GT). Event-related spectral perturbations from the midline and right-sided frontocentral sites showed CNTRL had decreased theta-power with increased beta-power on discordant trials containing TST words, an effect not seen in TA. Interestingly, the left-sided frontocentral sites did not show significant differences between TA and CNTRL on any trial type. Taken together, these results suggest that the presentation of TST words disrupts attentional control specifically on trials requiring the reorienting of attention in TA students. The lack of an AB towards TST words may be due to a 'ceiling' effect (TA are faster than CNTRL on all trial types). Alternatively, the lack of an AB towards TST may be because TA are able to disengage attention from threat (previously shown in our lab using a rapid serial visual presentation task) despite the disrupted attentional control during attentional reorienting.

Disclosures: E.A. Facundus: None. **E.A. Bourassa:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.05/II1

Topic: G.08. Other Psychiatric Disorders

Title: Prevalence of Post SSRI Sexual Dysfunction (PSSD) among 15-29 years old sexual and gender minorities in Canada and the US

Authors: *P. MARINHO[1], Y. PIRANI[2], J. DELGADO-RON[3], E. GREY[4], T. SALWAY[3]; [1]Western Univ. Canada, London, ON, Canada; [2]Willow Leaf Counselling, Vancouver, BC, Canada; [3]Simon Fraser Univ., Vancouver, BC, Canada; [4]Canadian Post-SSRI/SNRI Sexual Dysfunction Society, Vancouver, BC, Canada

Abstract: Selective serotonin reuptake inhibitors (SSRI) are a class of drugs commonly used as treatment for a variety of psychiatric disorders, such as depression, anxiety, obsessive-compulsive disorder, and panic disorder. Post-SSRI Sexual Dysfunction (PSSD) has been increasingly identified in recent years as an iatrogenic syndrome of enduring sexual dysfunction following the use and discontinuation of some antidepressants. Data on incidence or prevalence of PSSD are scarce. We aimed to describe the frequency of PSSD symptoms and the overall PSSD prevalence among sexual- and gender-diverse youth residing in Canada and the United States. This study uses direct standardization methods to estimate the sex-assigned-at-birth-specific prevalence of PSSD among past users of antidepressants. We used a subsample of UnACoRN, a binational survey of mostly sexual diverse youth aged 15 to 29 years. Participants reporting past use of antidepressants were included. We excluded current users. Upon adjusting for age, past or current use of gender-affirming hormonal therapy, and past use of antipsychotics, we found persisting symptoms of sexual dysfunction upon treatment discontinuation in 14.36% of those assigned male at birth (95% CI: 8.24% to 20.49%) and 26.24% of those assigned female at birth (95% CI: 22.51% to 29.97%). Regarding PSSD-specific symptoms, genital hypesthesia (43.1%), erectile dysfunction (44.9%), pleasureless or weak orgasms (44.3%) and less desire for sex (40.2%) persisted after discontinuation of the SSRI. Many people benefit from SSRI medications; however, they may cause persistent symptoms of sexual dysfunction among approximately 1 in 4 youth assigned female at birth and 1 in 7 youth assigned male at birth. Transparency about the risks and meaningful informed consent are central to reducing this risk, particularly among people who are at an early stage of sexual development or whose sexual functioning is already compromised, as well as their care providers.

Disclosures: P. Marinho: None. **Y. Pirani:** None. **J. Delgado-Ron:** None. **E. Grey:** None. **T. Salway:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.06/II2

Topic: G.05. Mood Disorders

Support: Office of Naval Research (ONR) N00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
Pritzker Neuropsychiatric Disorders Research Consortium

Title: Stress, Genetics and Mood: Impact of COVID-19 on a College Freshman Sample

Authors: *C. TURNER[1], H. KHALIL[3], V. MURPHY-WEINBERG[1], M. H. HAGENAUER[2], L. GATES[1], Y. TANG[1], L. WEINBERG[1], R. GRYSKO[1], L. FLORAN-GARDUNO[1], T. DOKAS[1], C. SAMANIEGO[1], Z. ZHAO[1], Y. FANG[1], S. SEN[1], J. F. LOPEZ[4], S. J. WATSON[5], H. AKIL[2];
[2]Univ. of Michigan, [1]Univ. of Michigan, Ann Arbor, MI; [3]The Univ. of Michigan, The Univ. of Michigan, Ann Arbor, MI; [4]Univ. Michigan, Univ. Michigan, Ann Arbor, MI; [5]Univ. of Michigan, Michigan Neurosci. Inst., Ann Arbor, MI

Abstract: Using a longitudinal approach, we sought to define the interplay between genetic and non-genetic factors in shaping vulnerability or resilience to COVID-19 pandemic stress, as indexed by the emergence of symptoms of depression and/or anxiety. University of Michigan freshmen were characterized at baseline using multiple psychological instruments. Subjects were genotyped and a polygenic risk score for depression (MDD-PRS) was calculated. Daily physical activity and sleep were captured. Subjects were sampled at multiple time points throughout the freshman year on clinical rating scales, including GAD-7 and PHQ-9 for anxiety and depression, respectively. Two cohorts (2019-2021) were compared to a pre-COVID-19 cohort to assess the impact of the pandemic. Across cohorts, 26%-40% of freshmen developed symptoms of anxiety or depression (N=331). Depression symptoms significantly increased in the pandemic years, especially in females. Physical activity was reduced, and sleep was increased by the pandemic, and this correlated with the emergence of mood symptoms. While Low MDD-PRS predicted lower risk for depression during a typical freshman year, this apparent genetic advantage was no longer evident during the pandemic. Indeed, females with lower genetic risk accounted for the majority of the pandemic-induced rise in depression. We developed a regression model that explained approximately half of the variance in follow-up depression scores based on psychological trait and state characteristics at baseline and contributed to resilience in genetically vulnerable subjects. This model is being tested on the 2021-2022 Freshman cohort and the results will be reported. We discuss the concept of multiple types of resilience, and the interplay between genetic, sex and psychological factors in shaping the affective response to different types of stressors.

Disclosures: C. Turner: None. **H. Khalil:** None. **V. Murphy-Weinberg:** None. **M.H. Hagenauer:** None. **L. Gates:** None. **Y. Tang:** None. **L. Weinberg:** None. **R. Grysko:** None. **L. Floran-Garduno:** None. **T. Dokas:** None. **C. Samaniego:** None. **Z. Zhao:** None. **Y. Fang:** None. **S. Sen:** None. **J.F. Lopez:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

PSTR098. Depression and Anxiety

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.07/II3

Topic: G.05. Mood Disorders

Support: NIH Grant DA051922

Title: Gray matter volumetric correlates of depression and polygenic risks in children: preliminary evidence from ABCD study

Authors: *Y. CHEN[1], X. LUO[1], J. S. IDE[1], X. FU[2], C.-S. R. LI[1];
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]The Second Xiangya Hosp. of Central South Univ., Changsha, China

Abstract: Genetic variants may confer risks for depression by modulating brain structure and function. Previous studies demonstrated cerebral volumetric correlates of depression, largely in moderate-sized samples. However, few have examined the shared and distinct neural correlates of depression and polygenic risks. Here, we followed published routines and performed voxel-based morphometry analysis of 6,186 unrelated subjects (2,774 girls, 9-10 years) curated from the Adolescent Brain Cognition Development project. For all subjects, we computed polygenic risk scores (PRS) for depression by using 33 UK Biobank cohorts of the Psychiatric Genomics Consortium as the base sample. We performed whole-brain regressions against depressive symptoms and PRS in a single model for boys and girls combined and separately, after controlling for age in months, sex (for boys and girls combined only), race, study site, scanner model, and total intracranial volume, and evaluated the results at a corrected threshold. In all subjects as well as boys and girls alone, more depressive symptoms were associated with smaller regional gray matter volumes (GMV) across frontal, parietal, temporal, occipital, insular and subcortical regions. In all subjects, and boys alone, higher PRS was associated with GMV reduction of frontal gyri, insula, and cerebellum, whereas no significant volumetric correlates of PRS were identified in girls alone. These findings collectively suggest shared and distinct cerebral volumetric bases of depressive symptoms and polygenic risks and potential sex differences in volumetric markers underlying polygenic risks for depression in children.

Disclosures: Y. Chen: None. **X. Luo:** None. **J.S. Ide:** None. **X. Fu:** None. **C.R. Li:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.08/II4

Topic: G.05. Mood Disorders

Support: NIH K01 MH108705

Title: The Effects of Exogenous Cortisol Administration on Positive Emotion Seeking Motivation in Major Depression

Authors: *K. SUDHEIMER[1], D. DUVIO[2], E. SHOLS[3], E. HEINEMEYER[4], D. JAMES[2], K. SILGE[1], Z. BENNETT[1], A. SCHATZBERG[2], R. O'HARA[2];
[1]Southern Illinois Univ., Carbondale, IL; [2]Stanford Univ., Stanford, CA; [3]Stanford Unioversity, Stanford, CA; [4]Palo Alto Univ., Palo Alto, CA

Abstract: Patients with depression (MDD) suffer from an attenuated experience of positive emotions. Feeling less positive emotions is closely tied to the motivation to engage in experiences that would generate positive emotions. However, the capacity to feel positive emotions and the motivation to seek out positive emotional experiences are not intrinsically linked.
Patients with MDD also commonly experience hypersecretion of cortisol and dysregulation of cortisol secretion. Cortisol signaling is physiologically intertwined with dopamine signaling, which underlies aspects of motivated reward behaviors.
We tested if a single dose of exogenous cortisol affected positive emotion-seeking motivation in MDD using a double-blind, placebo-controlled crossover design. Participants completed a lever-pressing (keyboard space bar) where they were rewarded with positive emotional pictures. The pictures were delivered on a randomized but discrete variable reinforcement schedule that included 1 picture for every 5-65 lever presses. The speed of lever pressing was logged for each trial as a proxy measure of motivation.
Two linear mixed-effect models tested the main and interactive effects of cortisol pressing speed. The first model investigated pressing speed changes across reinforcement levels. The second model tested how participants' motivation was affected by winning or losing streaks.
The first model results showed main effects of gender (males greater than females) and diagnosis (MDD greater than healthy). The results also suggest that cortisol did not affect everyone in the study uniformly. We observed a drug-by-diagnosis interaction, where cortisol slightly increased the lever pressing speed of patients with MDD, but had no effect on healthy participants. Curiously this effect occurred on a background main effect of patients with MDD pressing slightly faster than healthy participants.
The second model also included factors for failure streak and success streak. The results indicate that repeated failures are associated with a linear decrease in lever pressing speed, and repeated successes are associated with non-linear increases in lever pressing speed. Once the number of successes exceeded ~18, cortisol caused a dramatic increase in lever pressing speed in patients with depression and a dramatic slowing of lever pressing speed in healthy participants.
Taken together these data suggest that patients with MDD seem to have surprisingly high positive affect motivation that is somewhat amplified by cortisol signaling.

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Poster

PSTR098. Depression and Anxiety

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Program #/Poster #: PSTR098.09/II5

Topic: G.05. Mood Disorders

Support: ONR 00014-19-1-2149
Pritzker Neuropsychiatric Disorders Research Consortium Fund, LLC
Hope for Depression Research Foundation

Title: The role of the HPA axis response to an acute social stressor in predicting resilience to anxiety and depression in college freshmen

Authors: *H. KHALIL[1], C. A. TURNER[2], V. MURPHY-WEINBERG[3], L. GATES[3], Y. TANG[3], L. WEINBERG[3], L. FLORAN-GARDUNO[3], K. ARAKAWA[3], J. F. LOPEZ[4], S. J. WATSON[5], H. AKIL[2];
[1]The Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, [3]Univ. of Michigan, Ann Arbor, MI; [4]Univ. Michigan, Univ. Michigan, Ann Arbor, MI; [5]Univ. of Michigan, Michigan Neurosci. Inst., Ann Arbor, MI

Abstract: The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in emotion regulation and stress coping. Here, we report the results of the HPA axis response to an acute social stressor, the Trier Social Stress Test (TSST), in a relatively healthy group of young adults with a view towards predicting psychological resilience. The TSST was administered to 246 University of Michigan freshmen (130 females, 116 males), and their heart rate, blood cortisol and ACTH levels were captured before, during and after the TSST. The subjects were genotyped and characterized at baseline using multiple psychological instruments and were subsequently sampled at various timepoints during their freshman year on clinical rating scales, namely the GAD-7 for anxiety and the PHQ-9 for depression. Initial results show that the shape of the cortisol and ACTH curves were different between those who did and did not have depression symptoms at the time of the TSST, with the depressed group showing a blunted cortisol and ACTH response to the stressor. Moreover, the subjects who developed depression and/or anxiety symptoms during their freshman year tended to have higher pre-TSST cortisol levels. In addition, the change in cortisol levels during the TSST significantly correlated with both baseline and follow-up PHQ-9 scores. Finally, we applied machine learning approaches to understand how the shape of the stress response curve differs. The Euclidean distance between the cortisol response of each subject with each other was calculated, and clustering was performed between subjects. Using a K-medoid clustering algorithm, we asked whether the clusters correspond to the group of subjects who did or did not develop depression symptoms during their freshman year. This simple clustering algorithm worked better than chance would predict. These results show the interplay between psychological and physiological measures in predicting vulnerability or resilience to mood disorders.

Disclosures: H. Khalil: None. **C.A. Turner:** None. **V. Murphy-Weinberg:** None. **L. Gates:** None. **Y. Tang:** None. **L. Weinberg:** None. **L. Floran-Garduno:** None. **K. Arakawa:** None. **J.F. Lopez:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.10/II6

Topic: H.01. Attention

Title: Threat alters theta/beta ratio during reorienting of attention in test anxiety

Authors: H. MATKINS[1], *E. A. BOURASSA[2];
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Abstract: Test anxiety appears to be similar to other forms of anxiety in some domains, but distinct in others. Previously, our lab found that participants with test anxiety had decreased efficiency of the orienting network of attention as measured with the Attentional Networks Task, which was an unexpected finding. In that experiment, electroencephalography (EEG) showed that test anxious participants (TA) had decreased beta-power on centrally cued trials compared to non-test anxious participants (CNTRL), whereas they had higher theta- and lower beta-power on spatially cued trials compared to CNTRL. As a decrease in the ratio between theta- and beta-power (theta/beta ratio, TBR) is associated with increased attentional control, these data suggested that TA had lower attentional control in their orienting network. To further characterize the differences between CNTRL and TA on the orienting network, 11 CNTRL and 9 TA participants (as determined by a computerized task developed and validated in our lab) completed a modified Posner task while 9-lead EEG was recorded. The task consisted of a 1 s central fixation, followed by the presentation of a cue for 0.1 s on the left or right of the fixation. 0.1, 0.2, 0.4, or 0.8 s following the cue, the target was presented, which could either be in a concordant or discordant position with respect to the cue. The modification was that the fixation could either be a central cross (CC), a non-threatening word (NT, such as DAYS or OPENING), or a test-specific threatening word (TST, such as QUIZ or FAILURE). Behavioral data showed that discordant trials took longer than concordant trials, and TA responded faster than CNTRL; similarly, accuracy was higher on concordant trials and for TA (all expected effects). There were no significant interactions between factors. On EEG, trials with CC or NT fixation showed that TA had lower theta-power 200-400 ms post-target than CNTRL without significant differences between concordant and discordant trials. On congruent trials with TST fixation, there was little difference between CNTRL and TA on EEG. However, on discordant trials compared to concordant trials, CNTRL had a significant decrease in theta-power (0-200 ms) and increase in beta-power (100-400 ms). TA, on the other hand, had an increase in theta-power (250-400 ms) without a change in beta-power. Taken together, these results suggest that threatening stimuli decrease TBR (increase attentional control) in CNTRL during the reorienting of attention. However, in TA, threatening stimuli increase TBR (decrease attentional control) during the reorienting of attention, specifically by increasing theta-power.

Disclosures: H. Matkins: None. **E.A. Bourassa:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.11/II7

Topic: G.05. Mood Disorders

Support: NIH Grant DA051922

Title: Gray matter volumetric correlates of the polygenetic risk of depression: a study of the Human Connectome Project data

Authors: X. FU[1,2], Y. CHEN[1], X. LUO[1], J. IDE[1], *C.-S. LI[1];
[1]Yale Univ., New Haven, CT; [2]The Second Xiangya Hosp. of Central South Univ., Changsha, China

Abstract: Genetic factors confer risks for depression. Understanding the neural endophenotypes, including structural brain metrics, of the genetic predisposition to depression would help in unraveling the pathophysiology of depression. We employed voxel-based morphometry (VBM) to examine how gray matter volumes (GMV) correlated with the polygenic risk score (PRS) of depression using the 1200 Subjects Release (S1200) dataset from Human Connectome Project (HCP). This dataset contains behavioral, genomic, and imaging data on young adults aged 22 to 35, who have largely passed the peak of neurodevelopmental but have not yet begun to manifest neurodegenerative changes. The severity of depression (depressive problems) was quantified in DSM-oriented scales of Achenbach Adult Self-Report. The PRS was computed using the Psychiatric Genomics Association Study as the base sample. After exclusion of subjects with missing information, a total of 993 individuals (53.6 % female) were included in this study. In multiple regression of PRS for depression, with age, gender, race, drinking severity, and TIV as covariates, regional GMVs in positive correlation with PRS were observed in bilateral hippocampi, the right gyrus rectus and olfactory cortex. Regional GMVs in negative correlation with the PRS were observed in a wide swath of brain regions, including bilateral frontal and temporal lobe, anterior cingulate cortex, thalamus, parahippocampi, cerebellum, and the left postcentral gyrus, cuneus, and amygdala. With the severity of depression problems included as an additional covariate, the findings did not significantly change. These findings add to the literature of volumetric reduction in depression by showing a more diverse pattern of the volumetric markers of the PRS of depression, with some regions showing higher but other regions lower GMV in link with the genetic risks of depression.

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Poster

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Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.12/II8

Topic: G.05. Mood Disorders

Title: Altered Functional Connectivity in Depressed Adolescents: Insights from the ABCD Study

Authors: *M. WAGNER[1], A. CAMASSA[2], Y. CHEN[3], B. LIU[1], T. J. SEJNOWSKI[4]; [1]Univ. of California San Diego, San Diego, CA; [2]The Salk Institue, La Jolla, CA; [3]Univ. of Washington, Seattle, WA; [4]Salk Inst., La Jolla, CA

Abstract: During adolescence, neurodevelopment occurs, and the brain becomes highly susceptible to both internal and external factors that can lead to neurological abnormalities. Numerous studies have identified abnormal connectivity associated with mental disorders in adults but little is known about adolescents. This is an important area of research as many mental disorders develop during adolescence and continue into adulthood. Specifically, major depressive disorder (MDD) stands out as a disorder that is prevalent in adolescents without a strong biological basis. Currently, the Diagnostics and Statistical Manual (DSM) is the "gold standard" for diagnostics, but the inter-rater reliability for adolescent depression is only a kappa of 0.28, deemed as "questionable".

In this study, we utilized neuroimaging data obtained from the Adolescent Brain Cognitive Development study (ABCD) at the baseline, including structural and functional MRI. Our sample consisted of 1429 healthy participants and 353 adolescents diagnosed with depression, all aged 9-10 years. We applied a novel deep learning seed-based segmentation algorithm called SynthSeg+ (citation) to each subject's structural MRI, resulting in 98 regions of interest (ROI) defined by the Desikan-Killany brain atlas. After applying this segmentation to obtain representative functional activity from the fMRI data for each ROI, we compute functional connectivity (FC). Conventional FC is often assessed by calculating symmetric pairwise covariance, which is unable to detect directional interactions and is biased by correlation. To overcome these limitations, we employed a new algorithm called dynamical differential covariance (DDC, citation). This method allows for the reliable and computationally sustainable estimation of directed causal interactions across brain regions, particularly in large datasets. Our findings revealed disrupted patterns of functional connectivity in adolescents with MDD compared to the control group. These alterations were observed at both the whole brain level and within functional subnetworks such as the Default Mode Network, Central Executive Network, and Salience Network, which aligns with previous studies (for a comprehensive review, see Mulders P.C. et al., 2015). These results contribute to a better understanding of the modifications in brain activity and connectivity induced by major depressive disorders, even at early stages. This highlights the importance of implementing early diagnostic strategies to prevent the occurrence of severe negative health outcomes and enhance the quality of life for adolescents, which can have lasting effects into adulthood.

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Poster

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Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.13/II9

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01MH127773

Title: Investigating reinforcement learning processes as machine learning forecasters of depression remission

Authors: *V. BANSAL[1], K. L. MCCURRY[2], J. LISINSKI[1], D.-Y. KIM[1], J. M. WANG[1], V. M. BROWN[3], S. GOYAL[1], S. M. LACONTE[1], B. CASAS[1], P. H. CHIU[4];
[1]Virginia Tech. Fralin Biomed. Res. Inst., Roanoke, VA; [2]Michigan Med., Ann Arbor, MI; [3]Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [4]Virginia Tech. Carilion Res. Inst., Roanoke, VA

Abstract: ***Objective*****:** We studied the potential of neural substrates of reinforcement learning (RL) to forecast remission status in clinical depression. ***Rationale***: Research has identified altered RL processes as a feature of depression. These processes may inform the course of depressive illness given links between the ability to update beliefs of the environment with change in mood symptoms such as anhedonia, anxious arousal, and negative affect. ***Methods***: We used support vector machines to test whether functional magnetic resonance imaging images of neural prediction error (PE) and neural expected value (EV) from a RL task could accurately classify participants on whether or not they would reach full remission at followup (~four months from baseline). Participants included 55 individuals (n=39 female) with a baseline depression diagnosis. We study whether anhedonia, anxious arousal, or negative affect moderate the ability for either of these classifiers to forecast remission. ***Results***: We are 95% confident that the neural PE (accuracy: 61.3%, 95% CI [57.7%, 64.8%]). and neural EV (accuracy: 69.8%, 95% CI [66.7%, 72.8%])) classifiers forecasted remission better than classifiers trained on permuted labels (which each recorded accuracy of 50.0%). Subsequently, we are 95% confident that the neural EV classifier performed significantly better than the neural PE classifier. We also found a significant effect when true remission status is regressed onto the interaction between neural PE-forecasted remission status and anhedonia scores (β = -0.30, p = 0.03): in a portion of non-remitting participants with high baseline anhedonia, the neural PE classifier incorrectly forecasts full remission. ***Conclusions***: We find that neural PE and neural EV are accurate, above-chance forecasters of remission and that reward representation is a better forecaster of symptom change than updating of expectations. Furthermore, this work shows that both neural PE and EV are viable biomarkers for symptom change independent of receiving treatment. Future directions in will target these neurobehavioral processes in behavioral interventions.

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Poster

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Program #/Poster #: PSTR098.14/II10

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH127773

Title: Domain-derived biomarkers of treatment response in major depressive disorder: an activation likelihood estimation meta-analysis of task-based neuroimaging

Authors: K. L. MCCURRY[1], V. M. BROWN[2], V. BANSAL[3], B. CASAS[3], ***P. H. CHIU**[3]; [1]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [3]Virginia Tech. Fralin Biomed. Res. Inst., Roanoke, VA

Abstract: ***Objective:*** The authors examined convergence across studies of neuroimaging treatment biomarkers within and across functional domains of major depressive disorder (MDD) in a functional magnetic resonance imaging (fMRI) meta-analysis. ***Rationale***: Functional neuroimaging research of individuals with MDD illustrates a diverse range of functional deficits, seen across various experimental paradigms. Additionally, research points to distinct patterns of activation associated with these differing functional domains. Previous meta-analyses have not considered this potentially significant source of heterogeneity in identifying treatment predictors. ***Methods:*** Using a PubMed literature search supplemented by reference lists from topical reviews, the authors identified research in which adults with MDD exhibited pretreatment neural responses predictive of subsequent clinical response to antidepressant medication or cognitive behavioral therapy. The authors performed activation likelihood estimation meta-analyses of peak voxel coordinates to identify fMRI activation consistently elicited by emotional tasks or resting states specifically, as well as activation consistently elicited across tasks. ***Results:*** The meta-analyses included 44 experiments of 974 unique participants. Across neuroimaging studies of negatively valenced emotion processing, significant convergence of baseline activation predictive of response to treatment was seen in the right anterior insula extending into the claustrum and in the subgenual anterior cingulate cortex extending into the head of the caudate. Across resting-state studies, no significant convergence of fMRI activation was seen. Meta-analyses of all fMRI activation yielded a cluster in the right anterior insula as convergent across studies, and the analysis of only activation linked with worse outcomes identified a similar but larger insula cluster. ***Conclusions:*** In adults with MDD, pretreatment responses in key limbic and paralimbic regions to negative emotional stimuli, a potential biomarker novel in its domain specificity, may provide vital information about subsequent clinical response. Furthermore, across different tasks, heightened pretreatment activation in the right anterior insula, a region central to switching between task-positive and resting states, emerged as a strong predictor of poor illness prognosis.

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Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.15/II11

Topic: G.05. Mood Disorders

Title: Biclustering algorithm applied to structural magnetic resonance imaging in major depressive disorder

Authors: *A. DE CASTRO PANZENHAGEN;
UFRGS, Porto Alegre, Brazil

Abstract:

Disclosures: A. de Castro Panzenhagen: None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.16/II12

Topic: G.05. Mood Disorders

Title: Individual Variation in the size of Salience Network relates to Depression

Authors: *S. KOIRALA[1], R. HERMOSILLO[1], A. ARRALE[1], E. FECZKO[1], J. LEIKAUF[2], O. MIRANDA-DOMINGUEZ[1], L. MOORE[1], K. WELDON[1], J. MOSER[1], S. NELSON[1], T. D. SATTERTHWAITE[3], J. ELISON[1], D. FAIR[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Stanford Univ., Stanford, CA; [3]Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The human cerebral cortex is organized into a tightly interconnected set of large-scale functional networks. Work using resting-state functional connectivity MRI has established a canonical network architecture that is broadly shared across the population. While the use of population average network topographies has yielded important discoveries, it obscures individual differences in brain network organization. Recent studies have revealed subject specific functional network topography, where individuals differ in terms of size of their functional networks. In fact, variation in topography of certain association networks relates to individual differences in cognition. However, it is an open question as to what topographic variation looks like in disorders such as depression. Depression is a major psychiatric disorder

associated with abnormal cognitive control and emotion regulation. Various functional brain networks, especially the salience network (SAL), have been implicated in depression. The SAL comprises the anterior insular cortex (AI) and dorsal anterior cingulate cortex (dACC) and is involved in detecting and orienting to both external and internal salient stimuli. Previous studies have shown heightened SAL response selectively to negative stimuli in depression and aberrant functional connectivity at rest. Lesions of the salience network have been associated with increased depressive symptoms. Given prior findings, we examined whether surface area of the SAL network is correlated with depression. Using data from the Adolescent Brain and Cognitive Development (ABCD) study (n = 5530), and the MIDB probabilistic atlases, we delineated person-specific functional networks and calculated their cortical surface area. Depression scores were extracted from the Child Behavior Checklist (CBCL). We hypothesized that the variability in the size of the SAL network would predict differences in depression scores. Controlling for gender, parental education, site, and total surface area, regression analyses showed that the surface area of the SAL network positively predicted depression score (p_{fdr} <0.05) such that individuals with higher depressive symptoms had larger SAL network. Post-hoc analyses revealed that no other network showed a significant relationship (p>0.05). Taken together with our prior work, we conclude that variability in functional network size, relates to individual differences in depression as measured by self-reported scores on the CBCL. Future work will work to replicate these findings in other large-scale datasets, and further investigate the correspondence of this finding with other measures of mood.

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Poster

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Program #/Poster #: PSTR098.17/II13

Topic: G.08. Other Psychiatric Disorders

Support: NIH K08MH080239
DOD W81 XWH-10-2-0181

Title: Transdiagnostic measure of psychopathology (p-factor) is associated with an increase in negative affect, a decrease in positive affect and constraint, consistent with the research domain criteria (rdoc) with the multidimensional personality questionnaire (mpq)

Authors: *P. MANNAVA[1], A. PAVULURI[1], D. BUTLER[1], C. RISCO[1], J. MILANDU[1], G. MELLO[1], B. HICKS[2], E. BERNAT[1];
[1]Univ. of Maryland, Col. Park, College Park, MD; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: ***Background.*** Transdiagnostic models are emerging as powerful frameworks to characterize psychopathology and related underlying biological systems. A transdiagnostic framework for psychopathology, HiTOP, categorizes psychopathology into two primary dimensions: internalizing (e.g., depression, anxiety) and externalizing (e.g., substance use, antisocial behavior, disinhibition). Recent research defines the shared variance between these dimensions as a general psychopathology factor (*p*-factor). We utilize RDoC, which examines biological systems, specifically positive valence (PV), negative valence (NV), and cognition (COG). Recent work with fMRI has suggested a transdiagnostic pattern of brain systems in relation to broad ranges of psychopathology, pointing to increases in NV, and decreased activity in PV, and COG systems. This project tests the hypothesis that the measure of HiTOP *p*-factor is associated with RDoC PV, NV, and COG systems using self-report measures, providing evidence for these relationships. For HiTOP we utilize validated questionnaires to index relevant INT and EXT problems, and the shared variance between them for *p*-factor. We employ the Multidimensional Personality Questionnaire (MPQ) to assess the activation of PV and NV systems, and cognitive control (a subcomponent of RDoC COG).***Method.*** RDoC is operationalized by utilizing the MPQ (Patrick et al., 2002), and HiTOP is operationalized by utilizing the externalizing (ESI-100, ESI-160; Krueger et al., 2007) and internalizing self-report questionnaires (shared variance between Zung Self-Rating Depression Scale and the State-Trait Anxiety Inventory; Inventory of Depression and Anxiety Symptoms) across four datasets (Total N= 691, age *M*=29.7, female=56.6%, White=76.7%). All datasets calculated the shared variance between their externalizing and internalizing variables to create the *p*-factor.***Results.*** The results supported the hypothesis that in relation to *p*-factor, PEM (t=-3.36) and CON (t=-9.62) are reduced, and NEM (t=19.67) is increased (all *p*-values < .001). Unique patterns for INT (PEM, t=-12.96; NEM, t=10.07; CON, t=3.54) and EXT (PEM, t=-4.96; NEM, t=15.77; CON, t=-9.44) were also observed.***Discussion.*** These results provide additional support for the idea that the RDoC biological systems are related to general psychopathology (*p*-factor) in the hypothesized directions. This motivates future efforts to link biological measures of these systems with *p*-factor, for which these MPQ findings may provide guidance. The observed effects also suggest the potential utility of using the MPQ diagnostically to assess system modulation to *p*-factor, INT, and EXT.

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Poster

PSTR098. Depression and Anxiety

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Program #/Poster #: PSTR098.18/II14

Topic: G.08. Other Psychiatric Disorders

Support: DOB W81 XWH-10-2-0181

Title: P3 amplitude reductions are associated with general psychopathology factor in a go/no-go task

Authors: *L. BLAISE[1], A. PAVULURI[1], P. MANNAVA[1], J. MILANDU[1], C. RISCO[1], D. BUTLER[1], S. FIX[1], N. B. SCHMIDT[2], E. BERNAT[1];
[1]Univ. of Maryland, Silver Spring, MD; [2]Florida State Univ., Tallahassee, FL

Abstract: ***Background***. P3 event-related potential (ERP) amplitude has been demonstrated to be reduced in relation to most psychopathology, including internalizing (INT;e.g., depression), and externalizing (EXT; e.g. substance use, antisocial behavior, disinhibition) behaviors. Advancing this broad work developed in the field, we recently demonstrated that P3 amplitude reduction (P3AR) is related to a measure of general psychopathology (cf. psychopathology factor; *p*-factor, reflecting general life impairment) (Bernat et. al, 2020), as developed by current dimensional models of psychopathology (Hierarchical taxonomy of psychopathology; HiTOP). While P3 amplitude contains mostly delta activity, recent work indicates most ERP amplitude measures contain a mixture of theta and delta. The present project extends work assessing P3AR in relation to p-factor, to include theta, as well as assessment in data from a go/no-go task, and from participants with elevated internalizing problems. ***Methods***. 271 subjects (55.7% female; mean age=35.75, SD=16.07; 30.6% veterans; 59.4% Caucasian) completed a questionnaire battery, multi-task protocol, including a go/no-go task, while data was collected from a 96-channel EEG. Participants met for elevated anxiety sensitivity (on the Anxiety Sensitivity Index, e.g. 79.2% met primary diagnosis for INT disorder, e.g., anxiety, depression, PTSD). Time-frequency principal component analysis extracted 3 delta and 2 theta components in go/no-go stimuli, we assessed those most overlapping the N2-P3 complex. Spearman correlations and robust regressions were conducted in R. ***Results***. Correlations with *p*-factor were generated for delta go (ns), no-go (-.15*), and go/no-go differences (-.11^{+}) and in theta go (-.14*), no-go (-.15*) and go/no-go differences (ns). Basic task assessment replicated that delta and theta amplitudes were increased in no-go relative to go task conditions (t=-8.02, t=-7.49, respectively). Regression models evidenced unique significant variance observed for delta in no-go and significant unique variance for theta across both tasks (go: delta: t=-.671, theta: t=-2.081*; no-go: delta: t=-1.397, theta; t=-2.223*). ***Discussion***. Correlations demonstrated a significant relationship between P3AR and *p*-factor in delta and theta. Go/no-go differences were significant in delta and not theta relating to *p*-factor suggesting they may serve unique processes within the go/no-go task. Elaborative processing showed a reduction in no-go but not go while early attention and salience was similarly diminished in go and no-go tasks, demonstrating separable processes of delta and theta. p< .10^{+}, .05*, .01**, .001***

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Poster

PSTR098. Depression and Anxiety

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Support: NIH T32 Grant GM136611
NIH BRAIN Inititative Grant UH3NS103549
NIH K01 Grant MH116364

Title: An intracranial neurofeedback platform to measure and modulate mood in human neurosurgical patients

Authors: *K. KABOTYANSKI[1], J. ADKINSON[1], G. BANKS[1], E. BARTOLI[1], K. BIJANKI[1], N. DIAB[1], N. GIRIDHARAN[1], W. K. GOODMAN[2], C. HACKER[1], S. MATHEW[2], R. MATHURA[1], V. PIRTLE[1], N. POURATIAN[3], N. R. PROVENZA[1], S. RAJESH[1], Y. REED[1], S. SHETH[1], A. WATROUS[1];
[1]Neurosurg., [2]Menninger, Psychiatry and Behavioral Sci., Baylor Col. of Med., Houston, TX; [3]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX

Abstract: The use of surgically implanted electrodes with deep brain stimulation (DBS) provides a unique opportunity to both stimulate and directly record from active human neural tissue. The increasing use of DBS for refractory psychiatric disease allows researchers to investigate the circuitry underlying mood, cognition, and behavior. Neurofeedback (NFB) is a method of assessing self-control of brain functions by measuring brain waves and providing a feedback signal in real-time. Here, we present a novel approach for causally manipulating human brain activity using real-time NFB. We have demonstrated that NFB can successfully be applied in neurosurgical patients implanted with intracranial electrodes for epilepsy and treatment-resistant depression (TRD) to volitionally enhance amplitude of a target neural signal. We collected a baseline recording of neural activity during a naturalistic experience, in which we allowed the patient to view YouTube videos as they pleased. We then selected neural signatures that maximally distinguished a desired cognitive state for NFB training and presented a visually intuitive cue for real-time feedback. Successful modulation of the target neural feature was rewarded with points to incentivize and easily quantify performance. Preliminary analyses suggest that patients acquired the ability to upregulate their brain activity, as indicated by increasing total number of points with each subsequent trial. Qualitative data collected after experiment completion indicate that patients found the task engaging and enjoyable. Notably, mood assessments collected before and after the experiment show improvement in mood following targeted NFB. These results show the potential of NFB as both an experimental and supplementary therapeutic tool, particularly in patients with affective symptoms. Advancements in our understanding of volitional control over brain activity has important implications for developing more personalized brain-computer interfaces (BCIs) and providing individualization to closed-loop DBS systems. Future work will include further analysis of neural responses, as well as improvements to the neurofeedback task protocol for administration in future patients with epilepsy and other psychiatric conditions.

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Poster

PSTR098. Depression and Anxiety

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Topic: G.08. Other Psychiatric Disorders

Support: DOD W81 XWH-10-2-0181

Title: P3 Amplitude Reductions are Associated with General Psychopathology Factor in an Oddball Task: Replication and Extension

Authors: *A. PAVULURI[1], L. BLAISE[1], P. MANNAVA[1], D. BUTLER[1], J. MILANDU[1], S. FIX[1], C. RISCO[1], B. SCHMIDT[2], E. BERNAT[1];
[1]Univ. of Maryland, College Park, MD; [2]Florida State Univ., Tallahassee, FL

Abstract: ***Background.*** Research on the comorbidity of disorders suggests that broader, dimensional constructs of internalizing (**INT**), externalizing (**EXT**), and thought disorder (**TD**) measures better underlie common mental health disorders. Shared variance across these dimensions has long been noted, suggesting an even broader general psychopathology factor (***p*-factor**). Our previous findings extend work in the field suggesting that P300 amplitude reductions (**P3AR**; P3: attention allocation, basic information processing, and working memory),

commonly seen in oddball paradigms, can be associated with broader INT and EXT factors -- and that the shared variance with *p*-factor accounts for a significant part of these associations. Additionally, P3 has generally been measured using time-domain, but work from our group and others have demonstrated that ERP activity is better understood as a mixture of separate theta and delta activity. This study aimed to determine if the *p*-factor relationship with P3 holds in a population with elevated INT problems and to analyze the unique variance of time-frequency theta and delta measures. ***Methods.*** 271 subjects (55.7% female; 59.4% White, 27.0% Black; mean age=35.75, SD=16.07; 30.6% veterans) completed a questionnaire battery and a multi-task protocol, including an oddball task, while data was collected from a 96-channel EEG system. Participants also met for elevated anxiety sensitivity (**AS**; i.e., by scoring at or above the community sample mean on the AS Index), and 79.2% met primary diagnosis for an INT disorder (e.g., anxiety, depression, PTSD). Time frequency principal component analysis extracted one component each in delta and theta for both novels and targets. Spearman correlations and robust regressions were conducted in R. ***Results.*** For *p*-factor, correlations were evidenced for delta-novels (*r*=-.23***), theta-novels (*r*=-.24***), delta-targets (*r*=-.14*), and theta targets (*r*=-.11†). Regression models evidenced significant shared variance in both targets and novels, with similar unique variance observed for delta across targets and novels, and significant unique theta for targets which was not observed in novels (Novels: delta: *t*=-1.87†,theta: *t*=-1.38; Targets: delta: *t*=-1.74†, theta: *t*=-2.05*). ***Discussion.*** *P*-factor evidenced P3AR in delta and theta, with largely shared variance across delta and theta in novel and target stimuli, and some potential unique variance across delta and theta for both stimuli. These findings provide support for previous work regarding *p*-factor and P3AR, with the notable extension of reviewing this relationship in a population with elevated INT problems. p< .10†, .05*, .01**, .001***

Disclosures: **A. Pavuluri:** None. **L. Blaise:** None. **P. Mannava:** None. **D. Butler:** None. **J. Milandu:** None. **S. Fix:** None. **C. Risco:** None. **B. Schmidt:** None. **E. Bernat:** None.

Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.21/II17

Topic: G.08. Other Psychiatric Disorders

Support: University of Illinois Research Board

Title: Neural and behavioral changes linked to resilience: Evidence from a cognitive-emotional training study

Authors: *K. HOHL[1], Y. REDDY[2], G. HO[2], P. BOGDAN[2], H. WEST[2], A. DAVIS[2], A. SEATON[2], I. CHEN[2], H. BERENBAUM[2], S. DOLCOS[2], F. DOLCOS[2];
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Abstract: Despite recent progress in understanding the neural and behavioral mechanisms of instructed emotion regulation (ER), little is known about the long-term benefits of systematic ER training. Established therapies have long focused on enhancing ER skills as a means to improve resilience. However, alarming increases in the prevalence of anxiety and depression, especially in the college population, create an urgency to identify alternative solutions through accessible ER training programs, based on integrative understanding of emotion-cognition interactions and their neural mechanisms. Here we tested a cognitive-emotional training intervention that incorporates the use of two ER strategies: *focused attention* (FA) and *cognitive reappraisal* (CR). During the 5-week long training, undergraduate students (N = 47) applied FA and CR to scenarios presenting emotional conflicts, constructed with both external (visual stimuli) and internal (autobiographical memories) cues. Participants were pseudo-randomized into either the ER training group or a waitlist control group. All participants completed a series of pre- and post-assessments, which included self-report measures and cognitive control tasks. A subset of participants (N = 31) also underwent collection of resting-state fMRI data. Preliminary results have shown behavioral improvements in psychological well-being and cognitive control through changes in negative affect, meaning-making, general self-efficacy, positive refocusing and working memory. Brain imaging results have shown increases in resting-state functional connectivity (rsFC) among areas linked to cognitive control and ER (e.g., between right dorsolateral prefrontal cortex/dlPFC and medial PFC), along with decreases in rsFC between cognitive control regions and perceptual areas (e.g., between the right dlPFC and left lateral inferior occipital cortex). Overall, these findings provide evidence that flexible use of FA and CR promoted by our ER training increases resilience across emotional challenges, as indicated by changes in behavior and neuroplasticity.

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Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.22/II18

Topic: G.08. Other Psychiatric Disorders

Support: NIH UH3NS103550-04S1
FDA IDE G130107

Title: Longitudinal effects of subcallosal cingulate deep brain stimulation on the resting electroencephalogram in treatment-resistant depression.

Authors: *T. NAUVEL[1], S. ALAGAPAN[2], M. OBATUSIN[1], S. HEISIG[1], J. DAHILL-FUCHEL[3], C. ROZELL[2], A. WATERS[1], H. MAYBERG[1];

[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Georgia Inst. of Technol., Atlanta, GA; [3]Univ. of Arizona, Tuscon, AZ

Abstract: Major depressive disorder affects approximately 14.8 million adults in the US. While most cases of depression are treatable, up to 10% of the patients do not respond to conventional interventions. Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) white matter is an emerging treatment strategy for such treatment resistant depression (TRD) with published studies demonstrating sustained long-term antidepressant effects in 73% of implanted patients. While long-term effects are generally maintained once achieved, clinical observation, ratings, and local LFP electrophysiological recordings in the SCC show that recovery appears to have multiple stages: depressed; first well (acute effects); rough (improved but unstable); and well (>50% Hamilton Depression Ratings Scale). The time course of these changes varies individually. Here we test if the resting EEG demonstrates comparable changes to the LFP and behavioral changes previously observed. EEG was recorded in two cohorts of TRD patients receiving chronic SCC DBS using two DBS systems: Medtronic Activa PC+S r (n=8) and Medtronic Summit RC+S (n=5). All patients were tested at 8 time points: before DBS implantation; 4 weeks post-implantation without ongoing DBS; once a month for 6 months during active stimulation. Recordings consist of 5-minute eyes open resting EEG (EGI, 256 channels), collected with bilateral stimulation ON and OFF. Changes in EEG power over time show that there are differential early (1 month) and late (2-6 month) band-specific EEG changes in the first PC+S cohort of patients which are replicated in the RC+S cohort. Resting EEG spectral clusters transitions from ‘sick’ to ‘well’ occur at similar timepoints as the LFP. Furthermore, coherence and weighted phase lag index measures show decreases with stimulation. These findings provide evidence that the resting EEG can identify distinct early and late response change patterns over the course of successful SCC DBS treatment for TRD. The similarity of the identified sick-well transitions using EEG to those previously identified in the SCC LFP recordings suggest a nonlinear evolution of SCC-cortical network changes over time with ongoing DBS. These findings invite further consideration of the role of serial resting EEG to identify treatment milestones that might guide treatment optimization.

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Poster

PSTR098. Depression and Anxiety

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Topic: G.08. Other Psychiatric Disorders

Support: JP20dm0107099
JP20dk0307077
JP21dk0307103

JP20km0105001
JP20km0105002

Title: Loci Associated with Postpartum Depression: A Genome-Wide Association Study

Authors: *X. LI[1,2], N. TAKAHASHI[4], A. NARITA[3], Y. NAKAMURA[4], M. SAKURAI-YAGETA[3], K. MURAKAMI[3], M. ISHIKURO[3], T. OBARA[3], M. KIKUYA[3], F. UENO[3], H. METOKI[3], T. NAKAMURA[3], N. WARITA[3], Z. YU[3], C. ONO[3], N. KOBAYASHI[3], S. KIKUCHI[3], F. NAGAMI[3], S. OGISHIMA[3], J. SUGAWARA[3], T. HOSHIAI[3], M. SAITO[3], N. FUSE[3], K. KINOSHITA[3], M. YAMAMOTO[3], N. YAEGASHI[3], N. OZAKI[4], G. TAMIYA[3], S. KURIYAMA[3], H. TOMITA[3];
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Abstract: Postpartum depression (PPD) is a depressed condition occurring after birth, typically within the first monthafter delivery. Despite the high prevalence and negative consequences of PPD, *very little is known aboutits underlying biology.* Although biological factors, including hormonal changes and genetic predispositions, are involved in the pathogenesis of PPD, *the risk loci or genes susceptible to PPD remain largely obscure.*To our knowledge, *no genetic association studies have identified loci significantly associated with PPD.* Herein, we report a successful outcome from *a genome-wide association study (GWAS) to identify the locisusceptible to PPD.* The largest ever cohort consisting of 12,193 perinatal women, including 1,702 subjectswith PPD was subjected to the GWAS analyses. PPD was evaluated based on self-report questionnaires, the Edinburgh Postnatal Depression Scale. Information regarding multiple factors which were known to beassociated with PPD were collected and utilized as *confounding factors of PPD*. Among the *potential confounding factors associated with PPD, the number of deliveries and the number of family membersliving together with the highest SHAP value* were detected as the *most influential confounding factors inpredicting PPD using random forest, gradient boosted tree, and light gradient boosting machine algorithms.* The GWAS analyses considering these important confounding factors indicated genome-wide significant *PPD-associated loci with P < 5e-08* in the genome regions within or upstream of *DAB1, UGT8, DOCK2, ZNF572, DIRAS2, ZNF618, PTPRM, and PDGFB. A meta-analysis of GWAS results* from the three cohorts indicated the following loci as significantly associated with PPD: *rs377546683 at DAB1 (1p32.2), rs11940752 near UGT8, rs141172317, rs117928019, rs76631412, rs118131805 at DOCK2 (5q35.1), rs188907279 near ZNF572, rs504378, rs690150, rs491868, rs689917, rs474978, rs690118, rs690253 near DIRAS2 (9q22.2), rs1435984417 at ZNF618, rs57705782 near PTPRM, and rs185293917 near PDGFB.* Interestingly, many of these genes have been reported to be *related with psychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder, and autism spectrum disorder.* Pathway analyses indicated that SNPs suggestively associated with PPD (P < 1e-03) were mostly over-represented in categories including *long-term depression, GnRH signaling, Glutamatergic synapse, Oxytocin signaling, and Rap1 signaling.* Thus, the current study *first identifiedgenetic risk loci of PPD which may enlighten the genetic structure underlying the pathogenesis of PPD.*

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Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.24/II20

Topic: G.08. Other Psychiatric Disorders

Title: Significant evidence of association between maternal COVID-19 infection during pregnancy and better postpartum mental health

Authors: *R. L. XU[1], A. LAVALLEE[1], J. WARMINGHAM[1], E. ARDUIN[1], M. KYLE[1], M. HUSSAIN[1], J. RUSSO[2], D. DUMITRIU[1];
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Abstract: Background: Pregnancy is a unique time when parents, and mothers especially, are presented with novel stressors that can negatively affect their mental health. These include both personal and environmental worries related to changing physiologies, social support, and concern for their future baby, among other factors. This led us to investigate whether the COVID-19 pandemic, a time of already higher negative mental health effects, impacted the mental health of recently pregnant women. Specifically, we assessed the relationship between maternal COVID-19 infection status during pregnancy on postpartum maternal mental health in a subset of mothers enrolled in the COVID-19 Mother Baby Outcomes (COMBO) Initiative. **Methods:** Analysis of variance (ANOVA) models were used to investigate the association between maternal mental health four to six month postpartum and maternal COVID-19 infection status during pregnancy. Maternal mental health was measured using six self-reported surveys (PHQ-9, PCL-5 symptoms related to COVID-19 stress, STAI-state, Perceived Stress Scale, and the Somatization and Anxiety subscales of the Brief Symptom Index) and COVID-19 infection status was assessed using at-home and clinical tests. The continuous maternal mental health scores of the six measures were combined to establish one latent factor using confirmatory factor analysis (CFA). This produced a standardized mental health factor score for which higher scores denote greater mental health symptoms. Data was analyzed from 773 mothers (520 were COVID-19 negative and 253 were COVID-19 positive during their pregnancy). **Results:** At a 5% level of significance, preliminary ANOVA models found significantly different effects of COVID-19 infection status on postpartum maternal mental health factor scores (p=0.028). Contrary to the working hypothesis, higher prevalence of internalizing and stress symptomatology were observed in mothers that were not infected with COVID-19 during pregnancy (mean difference of 0.1888 standard deviations). These results will be supported with data collected from a supplemental substudy to COMBO. **Conclusion:** Preliminary results suggest that are significant improvements in maternal mental health four to six months

postpartum in mothers infected with COVID-19 during pregnancy compared with those who were not infected.

Disclosures: **R.L. Xu:** None. **A. Lavallee:** A. Employment/Salary (full or part-time):; Columbia University. **J. Warmingham:** A. Employment/Salary (full or part-time):; Columbia University. **E. Arduin:** None. **M. Kyle:** A. Employment/Salary (full or part-time):; Columbia University. **M. Hussain:** A. Employment/Salary (full or part-time):; Columbia University. **J. Russo:** None. **D. Dumitriu:** A. Employment/Salary (full or part-time):; Columbia University.

Poster

PSTR098. Depression and Anxiety

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Support: General Research Fund (GRF): 11103220 (J.H.)
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Innovation and Technology Fund (ITF), Hong Kong: MRP/053/18X (J.H.)
Health and Medical Research Fund (HMRF), Hong Kong: 31571096 (J.H.)

Title: Potentiated GABAergic neuronal activities in the basolateral amygdala alleviate stress-induced depressive behaviors

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Abstract: Aims: Major depressive disorder is a severe psychiatric disorder that afflicts ~17% of the world population. Neuroimaging investigations of depressed patients have consistently reported the dysfunction of the basolateral amygdala in the pathophysiology of depression. However, how the BLA and related circuits are implicated in the pathogenesis of depression is poorly understood. **Methods**: Here, we combined fiber photometry, immediate early gene expression (c-fos), optogenetics, chemogenetics, behavioral analysis, and viral tracing techniques to provide multiple lines of evidence of how the BLA neurons mediate depressive-like behavior. **Results:** We demonstrated that the aversive stimuli elevated the neuronal activity of the excitatory BLA neurons (BLA^{CAMKII} neurons). Optogenetic activation of CAMKII neurons facilitates the induction of depressive-like behavior while inhibition of these neurons alleviates the depressive-like behavior. Next, we found that the chemogenetic inhibition of GABAergic neurons in the BLA (BLA^{GABA}) increased the firing frequency of CAMKII neurons and mediates the depressive-like phenotypes. Finally, through fiber photometry recording and chemogenetic

manipulation, we proved that the activation of BLA^{GABA} neurons inhibits BLA^{CAMKII} neuronal activity and alleviates depressive-like behavior in the mice. **Conclusion:** Thus, through evaluating BLA^{GABA} and BLA^{CAMKII} neurons by distinct interaction, the BLA regulates depressive-like behavior.

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Poster

PSTR098. Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.26/II22

Topic: H.10. Human Learning and Cognition

Support: NARSAD Young Investigator Award (EVG)
National Center for PTSD

Title: Biases in hippocampal and striatal learning in trauma and post-traumatic stress disorder

Authors: *D. T. NGUYEN[1], J. H. KRYSTAL[2], E. V. GOLDFARB[1];
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Abstract: Post-traumatic stress disorder (PTSD) is a serious mental health condition that may develop after experiencing life-threatening or traumatic events. One feature of PTSD is impaired hippocampal function, which may lead to memory deficits like difficulty recalling details of past experiences. Notably, prior literature has shown that stress can also enhance striatal function, increasing learning for stimulus-response associations such as those underlying “habits”. However, whether this learning bias occurs in any individuals who experience traumatic events, or only those who go on to develop PTSD, is unclear. In this ongoing study, we are recruiting patients with PTSD (current N = 12/35) as well as trauma-exposed individuals who did not develop PTSD (trauma control [TC], N = 15/35) to perform a validated task that measures both

hippocampal and striatal learning during an fMRI scan (Goldfarb, Chun & Phelps, 2016). In this task, participants were instructed to find a target (a letter T) amongst distracting shapes (rotated letter Ls) and indicated the target's orientation. The task has two types of trials: context trials, in which repeated spatial layouts assist with finding the target (dependent on the hippocampus), and stimulus-response (SR) trials, which contain a color cue that probabilistically indicates the target's location and orientation (involving the striatum). To see which association was preferred, we also included combined-cue trials in which participants could use either context or SR cues and assessed which one participants used. Past findings show that acute and lifetime stress elicit a bias toward SR memory. We hypothesized that participants with PTSD would have impaired hippocampal-dependent context memory and preferentially engage striatal-dependent SR memory. Preliminary results are largely consistent with this hypothesis. Overall, participants in both groups learned SR and context associations and improved over time, though the PTSD group was overall slower. Critically, in combined-cues trials, the TC group was more likely to use context memory, but the PTSD group was not. Ongoing analyses will investigate the neural mechanisms underlying these learning biases. These preliminary data suggest that individuals with PTSD show specific learning biases that differ from those arising from trauma exposure alone.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Program #/Poster #: PSTR099.01/II23

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH12974
Health Research Board Grant HRA-POR-324
Irish Research Council Postgraduate Scholarship

Title: How do Medications and Symptom Severity Relate to Brain Connectivity in Bipolar Disorder: A 16-Site International Study

Authors: *L. NABULSI[1], M. J. Y. KANG[1], N. JAHANSHAD[1], P. M. THOMPSON[1], O. A. ANDREASSEN[2], C. R. K. CHING[1], D. M. CANNON[3], &. THE ENIGMA BIPOLAR DISORDER WORKING GROUP[1];
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Abstract: Bipolar disorder (BD) may be considered a dysconnection syndrome, involving disruptions to emotion-regulatory and reward-related circuitries. Network neuroscience can test neuroanatomical dysconnectivity in brain disorders, but limited sample sizes, variations in analysis techniques, and models neglecting effects of medication, have hindered reliability of

findings. In the largest graph theory analysis of structural brain connectivity in BD to date, we investigated global network-level differences in individuals with BD relative to healthy controls, and examined associations with medications and clinical features. We combined ENIGMA-standardized subject-specific nodal parcellation/segmentation and non-tensor-based tractograms derived from a high angular resolution diffusion-weighted approach. We generated structural connectivity matrices, both unweighted and weighted (by streamline count and fractional anisotropy). We included 449 individuals with BD (33+/-13 years, 55% F) and 510 healthy individuals (36+/-13 years, 62% F) from 16 international sites. All results were adjusted for multiple comparisons (pFDR<.05). After accounting for age, sex, and scan site, individuals with BD showed lower connectivity density, efficiency, longer paths, and higher centrality compared to controls (d=0.18-0.20). In the BD group, illness duration was significantly associated with differences in connectivity density, efficiency, path length and centrality. Age of illness onset was negatively associated with path length and efficiency in BD. Further investigations into short/longer duration of illness and early/later age of illness onset showed different connectivity trends in BD. Lower connectivity density, efficiency, and higher centrality was associated with a history of psychosis in BD, relative to those without a psychosis diagnosis, even when adjusting for medications. Greater number of manic and/or depressive episodes was not significantly associated with any network metrics. While lithium, anticonvulsants and antipsychotics were not significantly associated with any of the considered network metrics, antidepressant use was associated with higher centrality in BD, even when adjusting for other medications. Our large-scale, multisite study provides supportive evidence for global dysconnectivity in BD that is not explained by psychotropic medication and appears to relate to clinical aspects of the BD course. Our findings may inform future global efforts to understand the impact of BD signs and symptoms on brain architecture and mood regulation.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Program #/Poster #: PSTR099.02/II24

Topic: G.05. Mood Disorders

Support: Health Research Board (HRA-POR- 324)
NIH Grant RF1AG057892
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NIH Grant R01MH129742

Title: White Matter Microstructural Abnormalities in Bipolar Disorder Unveiled by Along-Tract Statistics: A Pilot Study

Authors: L. NABULSI[1], *B. Q. CHANDIO[2], G. MCPHILEMY[3], F. M. MARTYN[3], B. HALLAHAN[3], C. MCDONALD[3], P. M. THOMPSON[4], D. M. CANNON[3];
[1]USC, USC, Marina del Rey, CA; [2]Keck Sch. of Med., USC, Marina Del Rey, CA; [3]Univ. of Galway, Galway, Ireland; [4]Keck Sch. of Med., Univ. of Galway, Marina del Rey, CA

Abstract: Diffusion MRI studies have reported microstructural white matter (WM) deficits in bipolar disorder (BD), specifically in fiber bundles involved in regulating emotional, cognitive, and behavioral aspects of the disorder. However, the spatial mapping of microstructural differences in specific brain regions has been limited. In this pilot study, we employed BUndle ANalytics (BUAN), a novel tractography analysis approach, to investigate fine-scale WM microstructural differences along specific bundles in individuals with BD compared to healthy controls. We analyzed cross-sectional 3D diffusion-weighted brain MRI data from 38 individuals with BD (age: 39+/-13 y; 43% F) and 49 healthy controls (age: 45+/-12; 76% F). Images were processed to correct for subject motion and eddy-current distortions. To account for crossing fibers within voxels, we used a deterministic constrained spherical deconvolution algorithm. Fractional anisotropy (FA), a measure of microstructural organization, was calculated at each voxel. Whole-brain tractograms were registered to a bundle atlas template, and bundle extraction was performed using RecoBundles and a standard WM tract atlas. For each extracted bundle, a tract profile consisting of 100 segments per subject was generated using BUAN. Group comparisons were conducted using Linear Mixed Models on bundle profiles to localize differences in FA between BD and controls, adjusting for multiple comparisons. Compared to controls, individuals with BD showed lower FA in specific regions (Fig.1). Our findings support previous reports of disturbances in anterior and commissural fibers in BD. These pathways connect brain regions that are crucial for emotional regulation, motivation, decision-making, and cognitive control, which are impaired in BD. This pilot study provides insights into the complexity and functional specificity of fiber groups within large white matter bundles. Research in larger samples is planned to replicate and expand on these findings in characterizing WM abnormalities in BD.

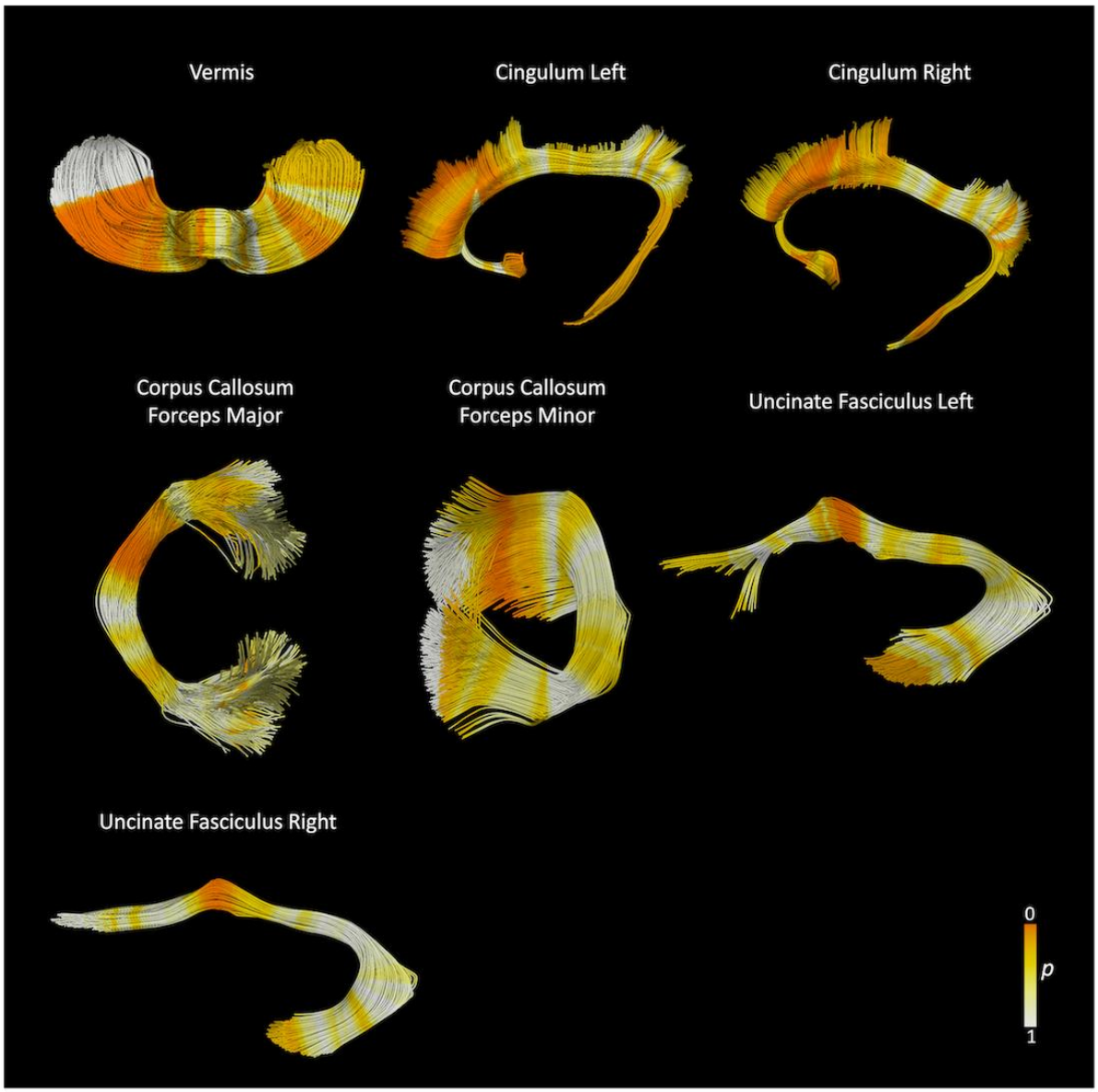

Figure 1. Localized White matter group differences in BD relative to healthy controls. Compared to controls, individuals with BD showed lower FA in specific region of the cingulum, fornix, arcuate, medial longitudinal fasciculus, uncinate fasciculus, and the corpus callosum (forceps major and middle portions). Within a narrow subregion, lower FA was observed in cerebellar pathways, while higher FA was found in brainstem (spino-thalamic) pathways. Other portions of the corpus callosum, as well as the right cingulum and uncinate bundles, did not exhibit significant group differences in FA.

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Poster

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NIH NIMH training grant T32MH019113 (G.H.)
Merit Award from the U.S. Department of Veterans Affairs (J.W.)

Title: Machine Learning to Predict Bipolar Disorder Using Multiple Modalities of Brain Magnetic Resonance Imaging

Authors: *L. R. DENG[1], E. J. BARSOTTI[1], A. J. WILLIAMS[1], G. E. CHRISTENSEN[1], M. W. VOSS[1], A. SALEEM[1], J. G. RICHARDS[1], L. SATHYAPUTRI[1], M. MANI[1], J. G. FIEDOROWICZ[2], J. D. LONG[1], J. XU[1], S. L. SCHMITZ[1], J. J. SHAFFER[3], J. A. WEMMIE[1], V. A. MAGNOTTA[1], G. I. S. HARMATA[1];
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Abstract: Bipolar disorder (BP) is a severe chronic psychiatric mood disorder. Its diagnosis is solely based on clinical assessments, and symptoms can overlap with other psychiatric disorders including depression and schizophrenia. An increasing number of studies have attempted to use machine learning (ML) to create predictive models for BP based on data from brain magnetic resonance imaging (MRI). However, most ML models have focused on measures from a single imaging modality and typically exclude the cerebellum. In this study, we sought to improve ML classification of participants with BP I and controls by combining information from structural, diffusion-weighted, and functional imaging of the cerebellum and forebrain. Participants with BP I and matched controls were recruited to an IRB-approved, multimodal imaging study. We obtained volumetric data (available for 131 BP, 81 control), diffusion-weighted neurite orientation dispersion and density imaging (NODDI) data (127 BP, 80 control), and resting state connectivity data (at the time of analysis, 86 BP and 52 control). For each of the three modalities, machine learning models were trained on all non-test subjects, and holdout validation was performed to select the best model, which was then used to classify the test set. The best model for each modality and its performance were (modality—model, test accuracy/ROC AUC/F1 score): volumetric—neural network, 0.814/0.760/0.846; NODDI—support vector machine, 0.732/0.667/0.784; connectivity—random forest, 0.864/0.812/0.914. The most important predictor variables involved the following areas: volumetric—distributed areas of cerebral cortex, corpus callosum, and right putamen; NODDI—cingulum, fornix, and inferior cerebellar peduncle; connectivity—right posterior cingulate cortex, right cerebellar tonsil, ventroposterior thalamus, and parts of temporal and parietal cortex. In addition, we combined the predictions of

the best model for each modality to determine how well BP can be predicted using all three modalities. Each model "voted" for the class of each test subject, with the strength of its prediction taken into account. The final predicted class was determined by the sum of the three models' votes. This resulted in an accuracy of 95.5%, ROC AUC of 0.969, and F1 score of 0.970. Voting with any 2 of the 3 modalities did not achieve metrics as high. In conclusion, BP versus control status can be predicted with a high degree of accuracy in this relatively small sample by combining structural, diffusion-weighted, and functional imaging data.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.04/II26

Topic: G.05. Mood Disorders

Title: Suicide attempt risk among adults with mental health emergency department visits.

Authors: *S. CHOI;
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Abstract: Suicide attempt risk among adults with mental health emergency department visits.AuthorsSeok-Ho Choi; Department of Psychiatry, Inha University Hospital, Incheon, Republic ofKorea.**DisclosuresSeok-Ho Choi**; None.**Abstract**Suicidal behavior is a serious public health problems and Korea's suicide rate is the highest in theOECD countries. Some studies have suggested that increased CRP (C-reactive protein) may be traitmarker of suicide attempts. We examined suicide attempt risk from mental health emergencydepartment (ED) visits by adults with suicide attempts or without.We investigated the semi-structured clinical charts of 509 adult patients between the ages of 18and 65 who visited mental health ED from January 1, 2022 to December 31, 2022. Suicide attemptwas defined as a self-damaging act carried out with some intent to die. Suicide attempt identificationand psychiatric interview were performed by a trained psychiatrist. All patients with CRP valuesgreater than 10 mg/L, malignant tumors, autoimmune diseases, or inflammatory conditions wereexcluded. We applied binary logistic regression models to analyze the data.Of the 233 patients included in the analysis, 153 were classified into the suicide attempt groupand 80 were classified into the non-suicide attempt group, and there was no sociodemographicdifference between the groups. As a result of the analysis, specific suicide plan, history of suicideattempt, history of psychiatric hospitalization, history of major depressive episode diagnosis, andhistory of psychiatric treatment were found to have a statistically significant effect on suicide attemptat the

significance level of 0.05. CRP levels were not statistically significant. The odds of attemptingsuicide increased 12.863 times if there was a specific suicide plan, 3.097 times if there was a historyof suicide attempt, and 2.608 times if there was a history of diagnosis of a major depressive episode.with a history of psychiatric hospitalization decreased the odds by 0.382 times compared to thosewithout, and with a history of receiving psychiatric treatment decreased by 0.302 times.In conclusion, we found that patients who received psychiatric treatment or hospitalization had alower risk of suicide attempt. In addition, CRP was found to have no effect on the risk of suicideattempt, unlike the results of previous studies.

Disclosures: S. Choi: None.

Poster

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Topic: G.05. Mood Disorders

Support: National Institute of Mental Health R01MH113230
American Foundation for Suicide Prevention STR-1-002-20

Title: Relationship between digital measures of rest-activity patterns and mood symptomatology in adolescents and young adults with bipolar disorder

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Abstract: The goal of this study was to evaluate whether digital actigraphy measures of rest-activity patterns would demonstrate a relationship to mood symptoms in adolescents and young adults with bipolar disorder (BD-AYA). Disturbances in rest-activity patterns are characteristic of BD and individuals with BD are sensitive to changes in these patterns, which can precipitate and worsen acute episodes. Rest-activity changes are often the earliest signs of episodes, preceding severe emotional changes. This has implicated circadian neurobiological mechanisms in the pathophysiology of BD and, supported by converging genetic and behavioral evidence, points to these mechanisms as key targets for prevention and treatment. Preventing episodes improves prognosis, especially early in the course of BD. Recent digital actigraphy methods hold promise for providing real-time passive data collection as a tool for both early detection and monitoring intervention changes. However, research on relationships with mood changes, particularly in young persons, is rare. This study aimed to use actigraphy to examine rest-activity patterns and how they relate to mood symptoms in BD-AYA. BD-AYA (N = 17, 53% female; mean age ± SD: 22.4±3.8 years) participated in a study (Brain Emotion Circuitry Targeted Self-Monitoring and Regulation Therapy, BE-SMART) of an intervention to regularize daily rhythms. They wore a GENEActiv wrist actigraph for two weeks and provided self-ratings on

the Quick Inventory of Depressive Symptomatology (QIDS) and the Altman Self-Rating Mania Scale (ASRM) at the start and end of the period. Three non-parametric measures of rest-activity patterns were analyzed: interdaily stability (IS: the consistency of day-night activity patterns), intradaily variability (IV: the fragmentation of rest and activity patterns), and relative amplitude (RA: the relative difference between the most and least active times of the day). Over two weeks, QIDS scores tended to decrease (t = -1.69, p = 0.05) and their changes were significantly correlated only with higher IS scores (r = -0.72, p < 0.001). Thus, more regular rest-activity patterns were associated with greater decreases in depressive symptoms. This supports salutary effects of regularity of daily rhythms on mood, and the potential use of digital actigraphy as a passive data collection measure that provides indicators of daily rhythm patterns salient to clinical symptoms. Actigraphy-derived measures of stability could help inform underlying neurobiological mechanisms of BD and be useful for the detection, treatment, and prevention of the disorder.

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Poster

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Topic: G.05. Mood Disorders

Support: NIH Grant R01 MH129742
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Title: Subcortical brain volume alterations in bipolar disorder: Associations with symptom severity and medication mode of action

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Abstract: Lower subcortical volumes have been reported in bipolar disorder (BD), but the impact of BD illness severity and medications in modifying brain volumes remains unclear. Here we evaluated BD-related subcortical alterations and their relationship to mood episodes and medication mode of action using 3D T1-weighted volumetric brain MRI acquired from 100 participants from the National University of Ireland Galway (BD=44, CN=56, 54% female).

Averaged left and right subcortical volumes of lateral ventricles, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens were derived from the ENIGMA-standard FreeSurfer (v5.3) protocol. Linear regression was used to test for BD vs healthy control (CN) differences, associations with number of mood episodes (hypo + manic; depressed), and type of medication including traditional indication-based categories and those based on pharmacological mode of action. Models included adjustments for age, sex, and intracranial volume. All results were adjusted for multiple comparisons.
In this sample, perhaps due to limited power, the BD group showed no detectable differences relative to CN on any brain volumes. In those with BD, taking antidepressants primarily targeting serotonin was associated with significantly smaller pallidum volumes (b=-196.2, p=0.035), and antidepressants targeting serotonin and other monoamines showed trending level effects in the same direction (b=-72.9, p=0.423). When all antidepressants were pooled, the effect was trending after controlling for other concomitant medications. A greater number of (hypo)manic episodes was associated with larger putamen and pallidum volumes (putamen b=61.6, p=0.020; pallidum b=25.8, p=0.0002) even when adjusting for medication use and duration of illness. Number of depressive episodes did not show detectable associations with volumetric differences.
Here, in a single-site sample of 100 participants, we found no significant subcortical differences between BD and CN. In those with BD, antidepressant treatment primarily targeting serotonin was associated with smaller pallidum volumes, and a greater number of (hypo)manic episodes was associated with larger putamen and pallidum volumes. These potential differential effects of manic episodes and medication on basal ganglia volumes will be tested in the larger, multisite ENIGMA-BD Working Group sample, and include analyses of clinical comorbidities and cross-disorder comparisons with those diagnosed with related mental illnesses.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.07/JJ1

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH129694

Title: Unveiling predictive neural circuit profiles for antidepressant response by integrating structural and functional connectivity

Authors: *X. TONG[1,2], G. FONZO[4], Y. ZHANG[2,3];
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Abstract: Major depressive disorder (MDD) is a prevalent condition that significantly affects the quality of life in both children and adults. Unfortunately, existing antidepressant treatments demonstrate limited effectiveness and unsatisfactory response rates. The development of effective therapies for MDD is hindered by the inadequately understood heterogeneity in MDD and its elusive underlying mechanisms. To address these challenges, we developed a multimodal fusion framework that leverages sparse canonical correlation analysis to collectively examine the alterations in structural and functional connectivity from pre-treatment magnetic resonance imaging (MRI) recordings. This innovative multimodal fusion procedure allows us to establish common space features of structural and functional connectivity, integrating information from both modalities to gain comprehensive insights into the complex interactions and abnormalities within the brain associated with MDD. We further linked multimodal connectivity features to the antidepressant response by integrating a neural network regression model into this framework, where the hidden layer in the neural network was designed to identify important neural circuits (combination of connectivity) for antidepressant response. Importantly, the parameters of the multimodal fusion procedure and the regression model were collectively trained to ensure that the fused connectivity features were directly relevant to antidepressant response. Using this approach, we successfully developed a prediction model for antidepressant response in 108 sertraline-medicated MDD patients and confirmed its generalizability through cross-validation ($r = 0.46$, R-squared = 0.21, $p_{permutation} < 0.001$). Our results revealed that the predictive neural connectivity profiles for sertraline response constituted four neural circuits associated to the cortical-subcortical limbic, corticostriatal, frontoparietal, and default-mode pathways. Specifically, functional connectivity in the default-mode pathway and structural connectivity in the corticostriatal pathway showed the most significant contribution to the sertraline response prediction. Overall, our findings demonstrate the potential of our multimodal framework to unveil predictive neural circuit profiles for antidepressant treatment response in MDD patients, providing valuable insights into the underlying mechanisms of treatment response heterogeneity and paving the way for personalized treatment approaches.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Program #/Poster #: PSTR099.08/JJ2

Topic: G.05. Mood Disorders

Support: R00HD099203

Title: Investigation of reward sensitivity as a buffer for pandemic-related externalizing and internalizing psychopathology across development

Authors: *C. MIKKELSEN[1], L. SOMMERVILLE[2], M. MAYES[3], R. MCCOLLUM[1], A. N. MELTZOFF[4], K. A. MCLAUGHLIN[2], M. L. ROSEN[1];
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Abstract: Previous work has linked exposure to both individual and community stressors, including stressors deriving from the COVID-19 pandemic, to the development of psychopathology in children and adolescents (Rosen et al. 2021, McLaughlin, 2022). Additional work has shown that sensitivity to reward can buffer against the development of psychopathology in instances of trauma and maltreatment (Dennison et al., 2016, Kasparek et al., 2020, Jenness et al., 2019). We seek to expand this research by testing the hypothesis that sensitivity to reward moderates the relationship between pandemic-derived stressors and the development of psychopathology. To test this hypothesis we recontacted participants from the Human Connectome Project in Development (HCP-D) during the pandemic (October 2021-January 2022) to have them complete about questionnaires regarding pandemic-related stressors (Rosen et al., 2021) and psychopathology (Strength and Difficulties Questionnaire; Goodman, 1997) We operationalize reward sensitivity as the differences in blood oxygen level dependent (BOLD) activity of the dorsal striatum, ventral striatum, and ventromedial prefrontal cortex for wins as compared to losses in the GUESSING task of the HCP-D. This work seeks to advance the understanding of protective factors that can mitigate the development of psychopathology in children and adolescents in the face of stressors.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

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Program #/Poster #: PSTR099.09/JJ3

Topic: G.05. Mood Disorders

Title: Machine learning based prediction of depression and anxiety in high school students

Authors: W. LO[1], ***B. NEPHEW**[1], S. LU[1], A. RODRIGUEZ[1], J. A. KING[2], D. KORKIN[2], R. LOPEZ[1], K. TYNAN[3];
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Abstract: With the recent rise in mental illness, especially in student populations, there is a critical need to develop targeted diagnostic and treatment tools. Given the tremendous variation in mental health symptomology across different populations, efforts to develop targeted intervention strategies may benefit from machine learning based predictive analyses. In this study, we investigate the accuracy of random forest classifiers (RFC) in predicting overall scores for depression and anxiety risk and identifying key risk factors from mental health and demographic data collected from 280 first year high school students. RFC were able to accurately (85-95%) predict depression and anxiety scores, and we identified substantial variation across gender and race in the key symptomology driving group specific predictions. This work underscores the need for group specific and/or personalized programming, preventative measures, and interventions for depression anxiety in adolescents.

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Poster

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Program #/Poster #: PSTR099.10/JJ4

Topic: G.05. Mood Disorders

Support: NIMH Grant 1K23MH112949-01

Title: Hemispheric divergence of interoceptive processing across psychiatric disorders

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Abstract: Conscious perception of the physiological status of the body involves interactions between the bottom-up receipt of visceral input and top-down attentional processes. Each of these processes has been associated with abnormal interoception across numerous psychiatric disorders, but the neural substrates for their functional convergence are unclear. Based on neuroanatomical arguments for the insula's unique position as a primary cortical interface for interoception, we hypothesized the dysgranular mid-insula to be a site of convergence between top-down and bottom-up processing streams and a region where disrupted interoceptive processing would be evident in psychiatric disorders. Forty-six individuals with anxiety, depression, and/or eating disorders (ADE) and 46 age-, sex-, and BMI-matched healthy comparisons (HC) completed two interoceptive tasks in the same 3T BOLD fMRI session: 1) a top-down task involving interoceptive attention to cardiorespiratory signals at physiological rest, and 2) a bottom-up interoceptive perturbation task involving double-blinded placebo-controlled

infusions of isoproterenol, a peripherally acting beta-adrenergic agonist that perceptibly increased cardiorespiratory arousal. A conjunction analysis of cluster-corrected group activation maps revealed coactivation within the insula across both tasks, but with hemispheric differences across groups. The HC group showed a greater proportion of coactivated voxels in the right dysgranular insula (chi-square = 26.7, $p<0.001$), while the ADE group did so in the left (chi-square = 26.7, $p<0.001$) and in a more dissimilar pattern to that of the HC's (Dice coefficient between groups: 0.78 in the right, 0.58 in the left). Across all participants, the perceived intensity of induced cardiorespiratory sensation was correlated with activity in the right dysgranular insula only ($R = 0.21$, $t=2.03$, $p<0.05$). Finally, examination of changes in whole-brain resting state functional connectivity (rsFC) of the unilateral convergent regions, from pre- to post-interoceptive tasks, showed increased FC between the right dysgranular convergent cluster and the left middle frontal gyrus in the ADEs but not HCs (voxel-wise $p<0.001$, cluster-corrected $p<0.05$), with the degree of rsFC change associated with trait anxiety and depression ($r=0.38$ and 0.43 respectively, p's<0.001). Taken together, these results suggest that an asymmetric hemispheric allocation of neural resources within the dysgranular insula during top-down and bottom-up cardiorespiratory interoception may be a 'locus of disruption' relevant for ADE psychopathology.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.11/JJ5

Topic: G.05. Mood Disorders

Title: Identification of Suicide Attempts Risk Factors in the UK Biobank

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Abstract: BACKGROUND: Suicide is a global public health challenge and a leading cause of death. However, considerable uncertainty remains regarding the association of multiple risk factors with suicidal behavior. The UK Biobank is a population-based cohort with extensive data across multiple domains. We sought to systematically screen and validate various behavioral and neurobiological risk factors for suicidal behavior in the UK Biobank. METHODS: Using large-scale datasets as a reference, we started with estimating polygenic risk scores (PRS) for suicide attempts in 337,138 participants from the UK Biobank. Phenome-wide association analyses were then conducted to identify factors associated with suicide-PRS, encompassing 836 factors from

behavioral (consisting of sociodemographic, lifestyle, early life and family history factors, mental health, physical measures, cognitive functions), neuroimaging, and blood and metabolic phenotypes across 11 different categories. Two-sample Mendelian randomization (MR) analysis was employed to further examine their potential causal relationships with suicidal behaviors. RESULTS: Out of the 836 factors examined, 265 factors were significantly associated with suicide-PRS, including 203 behavioral characteristics, 42 blood and metabolic biomarkers, and 20 brain traits. Among these, the behavioral measurements, particularly mental health and lifestyle factors, exhibited stronger associations. Importantly, MR evidence further supports 66 of these behavioral factors have a causal effect on suicidal behaviors, where, for instance, higher levels of maternal smoking around birth, smoking, neuroticism, sleep problems, and depressive symptoms, as well as lower levels of fluid intelligence and overall health rating. We also identified 10 blood and metabolic biomarker showing a causal effect, such as the white blood cell count and C-reactive proteins. Brain structures such as the insula also indicate a potential causal effect on suicidal behavior. CONCLUSIONS: This is the first study to comprehensively assess and validate a broad range of risk factors for suicidal behavior. The findings provide a list of phenotypes that have a causal impact on suicide attempts. The integration of genetic, behavioral, and neurobiological information holds promise for improving the prediction and prevention of suicidal behavior.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Topic: G.05. Mood Disorders

Support: NIH RF1 MH116920

Title: Brain changes associated with depression treatment: a meta-analytic informed investigation

Authors: *G. M. PEREZ[1], B. ROSENBERG[2], W. XU[3], D. J. OATHES[1];
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Abstract: Despite a variety of depression treatments, there is still a lack of consensus regarding what exact brain changes are associated with a treatment response. There is a growing body of literature in which neuroimaging is being used to further assess the brain impacts of various depression treatments. While a majority of work has focused on identifying brain activity differences between depression patients and healthy controls, there has been less investigation on brain activity changes occurring within a depression patient population before and after receiving treatment. Understanding changes within patients is critical to understanding treatment

mechanisms, and thus how to improve existing treatments. In order to investigate and synthesize current findings regarding brain changes in depression patients, I conducted a coordinate based meta-analysis of depression treatment neuroimaging studies to determine if there was convergence on any brain regions that changed in response to depression treatment across studies. Activation likelihood estimation was performed using GingerALE software to determine statistically significant brain regions. The meta-analysis included 15 different studies which resulted in data from 87 foci across 20 different experiments. The studies used various depression treatments including pharmacology, psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and ketamine as well as various emotion recognition tasks in the scanner. Across these studies, the right amygdala (MNI coordinates 30, 2, -22) was a region of significant convergence ($p<0.001$), meaning that this area was associated with a change in activity after patients received depression treatment. Upon further investigation, one of the strongest effects driving this finding was that right amygdala activity decreased after treatment. Qualitatively, many of the studies reporting an activity decrease were studies that involved a response to emotionally negative stimuli. Given that this meta-analysis was focused on depression patients, this finding offers a new perspective and support for the role of the amygdala in depression treatment and offers researchers a potential therapeutic target. Future work will focus on determining which brain networks this amygdala area engages with and how they might be manipulated using noninvasive neuromodulation to improve depression treatment outcomes.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Topic: G.05. Mood Disorders

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Title: Relationship between glutathione and age in the anterior cingulate gyrus of patients with major depression and healthy controls using 7T MR spectroscopy

Authors: *Y. YOSHIHARA[1], T. OKADA[3], T. SUWA[2], T. MURAI[2];
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Abstract: Glutathione (GSH) is one of the main antioxidants that plays a critical role in maintaining redox balance of the brain against oxidative stress. In patients with depression,

previous studies showed the reduction of GSH-related enzymes in peripheral blood, and the reduction of GSH in the frontal lobes of the postmortem brain. However, it is still unclear whether abnormality in GSH plays a pathophysiological role in depression. In addition, the relationship between GSH and age remains unclear, although human-aging is thought to be associated with oxidative stress. MR spectroscopy (MRS) is a noninvasive imaging modality that can assess the concentration of metabolites of brain. Using MRS, we examined GSH as well as other metabolites in the brain, and investigated their correlations with age in the patients with major depressive disorders (MDD) and healthy controls (HC). Twenty-four medicated patients with MDD (mean 45.1 y.o.) and 29 HC (mean 49.9 y.o.) were recruited, and scanned on an investigational whole-body scanner (MAGNETOM 7T, Siemens). Using proton MRS, we measured the concentration of neurochemical metabolites in the anterior cingulate cortex (ACC) with a STEAM sequence. Spectral analysis was carried out using LCModel (version 6.3-1L) on Windows 10. Neurochemicals that attained %SD ≤ 20 in more than 80% of subjects were included for further analyses. Segmentation was conducted for grey matter, white matter and cerebrospinal fluid to correct water-referenced concentration estimates. Between MDD and HC, no statistically significant difference was observed in the concentrations of GSH and other metabolites. There was a significant correlation between GSH and age in HC (R^2 = 0.1542, P = 0.0351), but not in MDD (R^2 = 0.0943, P = 0.1541). We suggest that redox balance against oxidative stress associated with aging may not be functioning adequately in MDD.

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Poster

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ZIAMH002778-17

Title: Individual differences in peripheral physiological arousal, and responses to exposure-based cognitive behavioral therapy in irritable youth: A pilot study

Authors: *T. ERJO[1], L. RUVOLO GRASSER[1], F. CHUKUNDAH[1], R. GERMAN[1], M. GOODWIN[2], W.-L. TSENG[3], J. WHITE[1], J. STODDARD[4], M. BROTMAN[1];
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Abstract: Objective: Irritability, an increased proneness to anger, is a primary reason youth present for psychiatric care, yet evidence-based treatments are limited. Our lab is implementing a clinical trial of exposure-based cognitive behavioral therapy (CBT) of anger-inducing events for youth with clinically impairing irritability. During exposure sessions, we measure peripheral psychophysiological indicators of arousal—heart rate (HR)—and regulation—heart rate variability (HRV) to predict treatment efficacy. We hypothesize that youth who exhibit higher HR and less HRV during the first exposure session will have less severe irritability by the end of treatment.
Rationale: Evaluate whether in-situ biosensing data provides peripheral physiological indicators of in-session response to exposures that identify which patients may be more likely to respond to treatment.
Methods: Participants were n=7 white, non-Hispanic/Latino/a/x youth (4 Males; M_{age}=10.57 years old, SD_{age}=1.62, $range_{age}$=9-13) with a primary disruptive behavior disorder (n=6) and/or an anxiety disorder (n=1) who underwent six sessions of exposures within a 12-session exposure-based CBT protocol. Participant HR and HRV were collected ambulatorily using the Empatica E4 wristband which records blood volume pulse using photophlethysmography. Motion artefact was removed by Empatica's algorithm for calculating inter-beat intervals. Beat correction was performed using Kubios ($M_{beats\ corrected}$=14.26%). Severity of irritability was determined by using the blinded clinician ratings of the Affective Reactivity Index. Two-tailed Pearson correlations were used to assess the relation between HR and HRV in the first exposure session (i.e., 'baseline') and post-treatment clinician-rated irritability, and symptom change.
Results: Preliminary pilot data indicate a moderate, positive association between HR during the initial exposure session (baseline) and clinician-reported irritability post-treatment (r=0.40, CIs:-.50,.89), and a small negative association between HRV and irritability (r=-0.23, CIs:-.84,.63). Participants who had higher HR at baseline exhibited larger reductions in irritability (r=-.26, CIs:-.85,.61). However, given sample size, we were underpowered to detect significant effects (all ps>0.05).
Conclusions: Peripheral psychophysiological data collection during exposure-based CBT using wearable biosensors is feasible in youth with clinically impairing irritability. Our pilot data highlight individual differences in HR and HRV. Subsequent analyses with a target sample of n=40 will investigate whether such variations predict treatment response.

Disclosures: T. Erjo: None. **L. Ruvolo Grasser:** None. **F. Chukundah:** None. **R. German:** None. **M. Goodwin:** None. **W. Tseng:** None. **J. White:** None. **J. Stoddard:** None. **M. Brotman:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.15/JJ9

Topic: G.05. Mood Disorders

Support: JP22dm0307002

Title: Unsupervised-based feature selection method robustly extracted resting state functional connectivity related to major depressive disorder

Authors: *A. YAMASHITA[1,2], Y. SAKAI[4,5], T. YAMADA[4,6], N. YAHATA[7,3,8,4], A. KUNIMATSU[9], N. OKADA[3], T. ITAHASHI[6], R. HASHIMOTO[10,6,4], H. MIZUTA[11], N. ICHIKAWA[12], M. TAKAMURA[12], G. OKADA[13], H. YAMAGATA[14], K. HARADA[14], K. MATSUO[15], S. C. TANAKA[4,16], M. KAWATO[4,17], K. KASAI[2,4], N. KATO[18], H. TAKAHASHI[19], Y. OKAMOTO[20], H. IMAMIZU[21,4], O. YAMASHITA[4,22];
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Abstract: Research on biomarkers for predicting psychiatric disorders from resting-state functional connectivity using functional magnetic resonance imaging has been advancing. While the discriminative performance of machine learning has been the main focus, determining which connections are important for classification has often been treated as a sub-goal. However, it is crucial to investigate the robustness of the selected connections because the selected connections are expected to utilize as a target of neurofeedback or transcranial magnetic stimulation therapy.In this study, we targeted major depressive disorder (MDD) and investigated the robustness of the extracted connections related to MDD using three types of feature selection methods. We used discovery data with 713 participants (149 patients with MDD) from 4 imaging sites and independent test data with 449 participants (185 patients with MDD) from 4 different imaging sites in SRPBS Multi-disorder MRI Dataset (https://bicr.atr.jp/decnefpro/data). We used regularization-based feature selection using machine learning such as LASSO (Regularization-based feature selection), univariate feature selection using t-test with multiple comparison correction (Univariate feature selection), and the unsupervised-based feature selection method using principal component analysis (PCA) that we proposed in this study. We extracted important connections using the discovery data and compared their effect sizes (difference between the MDD group and healthy control group) between the discovery and test data. We found that the unsupervised-based feature selection method robustly extracted functional connections with larger effect sizes in the test data (Cohen's d = 0.42) compared to other types of method (0.25 for regularization-based feature selection and 0.37 for univariate feature selection). Furthermore, the unsupervised-based feature selection selected 87 connections in the discovery data, and 12 of them were also extracted when performing feature selection using the test data. These connections were mainly related to thalamus and motor network. On the other hand, regularization-based feature selection did not find overlap connection and univariate feature selection found too many connections (over 200), making interpretation difficult. Previous study

reported that deep brain stimulation targeting the thalamus induced depressive symptoms, suggesting that the thalamus may be a potential cause of depressive symptoms. Our current results show that unsupervised-based feature selection method robustly extracted functional connections that are the cause of depressive symptoms.

Disclosures: **A. Yamashita:** None. **Y. Sakai:** A. Employment/Salary (full or part-time):; XNef, Inc.. **T. Yamada:** None. **N. Yahata:** None. **A. Kunimatsu:** None. **N. Okada:** None. **T. Itahashi:** None. **R. Hashimoto:** None. **H. Mizuta:** None. **N. Ichikawa:** None. **M. Takamura:** None. **G. Okada:** None. **H. Yamagata:** None. **K. Harada:** None. **K. Matsuo:** None. **S.C. Tanaka:** None. **M. Kawato:** A. Employment/Salary (full or part-time):; XNef, Inc.. **K. Kasai:** None. **N. Kato:** None. **H. Takahashi:** None. **Y. Okamoto:** None. **H. Imamizu:** None. **O. Yamashita:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.16/JJ10

Topic: G.05. Mood Disorders

Support: R01MD011746

Title: Decreased abundances of Neisseria in the oral microbiome aligns with increased depressive symptoms during pregnancy

Authors: *O. AGRANYONI[1], T. ROWLEY[1], S. JOHNSON[1,2], R. YOLKEN[1], S. SABUNCIYAN[1];
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Abstract: Oral microbiome dysbiosis has been linked to systemic disease with an underlying inflammatory etiology. However, the possible role of the oral microbiome in depression during pregnancy has received little attention. Thus, this study examines, for the first time, the composition of the salivary microbiome of women with depressive symptoms during pregnancy (n=46) compared with control women without depressive symptoms (n=327). Depressive symptoms were evaluated using the Center for Epidemiological Studies-Depression Scale (CES-D) (range: 0-60). A score of 16 or greater indicates clinically significant depressive symptoms. Using 16S rRNA next-generation sequencing, we found that CES-D scores were associated with differences in bacterial biomarkers of the salivary microbiome. Nine bacterial taxa were significantly decreased among women with depressive symptoms, including the Neisseria genus, which is associated with oral health and negatively correlated with pro-inflammatory cytokines and lower infant birth weight. Body mass index, smoking, oral health problems, and gestational week did not explain these differences. Thus, the bacterial differences found in women with depressive symptoms compared to controls appear distinct to this group. Moreover, using

prediction tools based on the 16S sequences, we found that several pathways of Menaquinol biosynthesis, a nitric oxide reductase, were decreased among women with depressive symptoms. In the absence of depressive symptoms, we found that bacterial diversity in pregnancy increased in the context of smoking and dental problems, and overall bacterial diversity was reduced in the third trimester. Our data suggest that the oral microbiome may provide insight into maternal internalizing symptoms during pregnancy. This information may inform future therapeutics and diagnostic tools.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.17/Web Only

Topic: G.05. Mood Disorders

Title: Identifying Eating Disorders in Adult Patients with Diabetes in a Hospital in México

Authors: A. PINEDA-DÍAZ[1], J. MONTEALEGRE PÉREZ[1], G. VILLAR-JUAREZ, Jr[2], ***I. JUAREZ-ROJOP**[3], I. SÁNCHEZ- PÉREZ[1], E. SANTOS-HERNÁNDEZ[1], G. NOLSCO-ROSALES[1], D. RUIZ-RAMOS[1];
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Abstract: Identifying Eating Disorders in adult patients with diabetes in a Hospital in México The existing evidence suggests that diabetes and eating disorders are related, these are disorders with multifactorial causes. Aspects of diabetes management which can increase the risk of eating problems include increased Body Mass Index (BMI), concerns about shape and weight, difficulty managing a long-term disease. The aim of this study was to identify eating disorders in patients with diabetes who attended a consultation at a hospital in Villahermosa, Tabasco, Mexico. This study transversal and descriptive. Demographic data were collected and anthropometric data (weight, height, Body Mass Index, body fat, waist, and hip circumference). In order to determine the presence of an eating disorder, the Eating Attitudes Test (EAT-26) was used as a questionnaire. Besides, blood samples are taken from each person via peripheral venipuncture for biochemical parameters (HbA1c, Triglycerides and Cholesterol). A total of 68 patients with diabetes were interviewed, of whom 47 (69.1%) had an eating disorder. They presented obesity (51.1%), overweight (29.8%) and 9 (19.1%) normal weight, mean years of diabetes was 24 for overweight/obese. Patients with obesity had a higher proportion of waist (108.83 cm), hip (114 cm), and body fat (40.7%) compared to the overweight group. Besides, these patients showed an increased HbA1c, Triglycerides and Cholesterol levels. In conclusion, we observe that more than half of the subjects with diabetes presented an eating disorder with

overweight/obese. This maybe an indication of the need for multidisciplinary management of patients with diabetes, in order to identify eating disorders and improve patients' quality of life.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.18/JJ11

Topic: G.05. Mood Disorders

Support: CIHR Vanier
Healthy Brains for Healthy Lives
CIHR
FRQS santé

Title: The relationship between the gut microbiome and host gene expression along the gut-vagal-brain axis in the context of healthy aging and depression: A single cell postmortem human survey

Authors: *S. BARNETT BURNS[1], J. SONG[2], V. YERKO[3], K. PERLMAN[2], R. DENNISTON[3], G. CHEN[3], O. MARTINEZ[4], M. DAVOLI[3], G. TURECKI[2];
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Abstract: We have evolved in a perpetual biochemical conversation with a complex gut microbial ecosystem whose collective genome is 100 times larger than our own, known as the gut microbiome. Studies in animal models suggest that the gut microbiome can modulate host gene expression regulation machinery in both the gut, and the brain, and thus may impact the both the enteric and central nervous system transcriptomes in humans as well. This paradigm shift has led to interest in the gut microbiome as a factor in multiple neurodevelopmental, neurodegenerative, and neuropsychiatric disorders, including depression. However, human data on these associations and the molecular pathways and mechanisms that may be involved is lacking. Using single cell RNA sequencing on postmortem human intestine and brain tissues from 28 donors (14 depressed and 14 healthy controls), we catalog cell types and map gene expression at 4 locations along the gut-vagal-brain pathways, from the cecum to the solitary nucleus and on to the insula or the substantia nigra. We further examine potential associations between gut microbiome 16S data from the same individuals and the gut-brain axis transcriptome in healthy aging vs depression and within individuals in order to gain insight on the potential of gut microbiome biomarkers for healthy aging and depression.

Disclosures: **S. Barnett Burns:** None. **G. Turecki:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

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Program #/Poster #: PSTR099.19/JJ12

Topic: G.05. Mood Disorders

Support: T32 NS105602
R01 NS111022
R01 NS117568
R01 NS123378
P50HD105353

Title: Limbic diffusion connectivity and pairwise machine learning classification of three affective phenotypes

Authors: *T. IMHOFF-SMITH[1], N. ADLURU[2], V. A. NAIR[2], A. ADLURU[2], A. L. ALEXANDER[2], B. HERMANN[2], A. STRUCK[2], V. PRABHAKARAN[2];
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Abstract: Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological disorders globally. Among the epilepsies, temporal lobe epilepsy (TLE) is the most common form in adults. In addition to recurrent seizures, TLE is associated with altered affect and increased occurrence of mood disorders, further disrupting quality of life. Disease progression has been associated with aberrant connections and reorganization of limbic structural connectivity. Despite these findings, previously presented analyses from our group demonstrated the challenges of predicting a single behavioral affect measure of fear using whole brain diffusion connectivity. In the current study, we identified discrete, multifaceted affective phenotypes of epilepsy and tested whether each could be distinguished from patients without epilepsy using measures of limbic structural connectivity and machine learning. Participants included 87 (mean age = 40.9 +/- 11.8 years, 52 female) patients with TLE and 25 (mean age = 36.4 +/- 11.5 years, 11 female) controls (C) from the Epilepsy Connectome Project. To identify affective phenotypes, we used k-means clustering on six behavioral measures of negative affect (adjusted for age and sex) from the NIH Toolbox across domains of anger, fear, and sadness. Structural connectivity measures were derived from multi-shell diffusion-weighted MRI (representing cross-sectional areas of fiber bundles connecting pairwise cortico-subcortical regions of gray matter) and adjusted for age and sex, from which we included 292 tracts with projections from the hippocampus or amygdala. To test model performance, we fit three pairwise support vector machine binary classification models (one for each phenotype) using a linear kernel with leave-one-out cross validation and extracted average feature weights to identify the most predictive features.Three patient clusters were identified: Typical (T; more similar to

controls), Atypical High (AH), and Atypical Low (AL) patterns of affect. Clusters respectively represented 45%, 22%, and 33% of patients. Support vector classification achieved performance of (AUC/accuracy) .64/66% (T vs. C), .52/53% (AL vs. C), and .52/52% (AH vs. C). Despite clear behavioral differences in high and low affective phenotypes, pairwise classification using limbic structural connectivity exhibited superior discriminant performance for the T cluster of patients. While there are detectable differences in limbic structural connectivity of epilepsy patients, aberrant affect may be driven by more complex biological features, non-linear brain-behavior relationships, or even nonbiological factors.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.20/JJ13

Topic: G.05. Mood Disorders

Title: Effects of three weeks electroconvulsive therapy on amygdala subnuclei volumes in patients with mood disorders

Authors: *E. B. KETTERER-SYKES[1,2], J. MACOVEANU[3,5], S. CRACIUN[6,2], K. MISKOWIAK[4,5];
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Abstract: Despite having greater success than traditional treatments and demonstrating response rates of up to 80%, electroconvulsive therapy (ECT) is largely underutilized in part due to its unclear mechanism of action (Grygylewski et al., 2013; Nordanskog et al., 2013; Pagnin et al., 2004). The aim of this structural magnetic resonance imaging (sMRI) study was to assess the effects of a three-week ECT treatment (8 sessions) in comparison to treatment-as-usual (TAU) matched control patients with major depressive disorder (MDD) or bipolar depression (BD) on hippocampus and amygdala volumes, as well as to assess group differences in individual hippocampal and amygdalar subregions, identify subvolumes correlated with symptom improvement following ECT, and explore the potential effects of ECT on prefrontal cortex volume and thickness. Both ECT (N=37) and TAU (N=40) patients underwent a Hamilton Depression Rating Scale 17-items (HRDS-17) survey pre- and post- treatment and an MRI investigation post treatment only. While a significant decrease of 36.9% in the HRDS-17 scores

of ECT patients was found ($p<0.001$), these scores were still greater compared to TAU patients ($p<0.001$). However, we observed a correlation between pre-treatment symptom severity and both symptom improvement ($r=-0.398$, $p=0.015$) and lower post-treatment symptom severity ($r=0.826$, $p<0.001$). We found a significant effect of treatment group on both the right ($F(64,9)=2.38$, $p=0.022$) and left ($F(64,9)=2.83$, $p=0.008$) amygdala subnuclei volumes, with ECT patients demonstrating significantly greater volumes of the lateral (left $p=0.004$, right $p=0.007$), basal (left $p=0.002$ and right $p = 0.041$), and paralaminar nuclei (left $p<0.001$ and right $p=0.001$), as well as the left corticoamygdaloid transition area (CTA) ($p=0.037$) compared to the TAU group. We did not observe an effect of ECT on hippocampal volumes and cortical thickness or volume. This study also found that adjusting for HAMD-17 accounted to a significant extent for the group differences observed in amygdala. There was however no significant correlation between symptom severity and amygdala volumes. The present study supports previous evidence that ECT produces an enlargement of amygdala volume, but contradicts results from studies assessing hippocampal volume and cortical thickness (Gryglewski et al., 2021). More research is needed to assess whether the observed changes in amygdala subnuclei volumes are relevant for clinical improvement or merely represent an epiphenomenon of electrical stimulation.

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Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

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Program #/Poster #: PSTR099.21/JJ14

Topic: G.05. Mood Disorders

Support: The National Research Foundation of Korea(NRF) grant funded by the Korea government (MSIT) 2017R1D1A1B04035829

Title: Cognitive effort discount in reinforcement and anterior insular cortex connectivity

Authors: *I. PARK;
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Abstract: *Introduction* The pathophysiology of anhedonia and amotivation in depressive disorder involved the dopaminergic reward pathway. The mechanisms of motivation can be operationalized by computational models of reinforcement learning which can help understand the underlying functional brain networks related to depression. *Method* Forty-five participants, including nine individuals with depressive disorder, completed affective assessments, and a computerized neurocognitive task and were scanned for resting-state functional MRI. Depression and avolition were assessed using the Beck Depression Inventory-II (BDI) and the Apathy

Evaluation Scale (AES). Effects of positive and negative reinforcement (PR and NR), cognitive burden, and temporal delay were examined using a reinforcement n-back task. We conducted model fittings and model comparisons of effort-based reinforcement models based on temporal difference learning, effort discounting, and loss aversion theory. The loss aversion model, two-learning rate model, and two-temporal discount rate model were compared using the Hierarchical Bayesian Inference (Piray 2019). Then correlation analyses of the affective scale scores and functional connectivity analysis with the estimated parameters from the best-fitting model were performed. *Results* The task performance was better in negative than positive reinforcement when the cognitive burden was low with temporal effort, whereas positive reinforcement performed better than negative reinforcement when the cognitive burden was high with temporal effort. The effects of reward type on effort were best represented by the loss aversion model. The BDI and AES scores correlated with the cognitive effort discount factor. The cognitive effort and temporal discount factors were associated with decreasing anterior insular cortex (AIC) and anterior cingulate cortex (ACC) and increasing nucleus accumbens and posterior middle temporal gyrus connectivities, respectively. The learning rate factor positively correlated with AIC and orbitofrontal cortex connectivities. *Conclusions* These findings demonstrated that motivations for reward acquisition and loss aversion are composed of learning, cognitive effort, and temporal discount processing. Among the effort-based reinforcement components, the cognitive effort discount reflects was associated with depression and amotivation. The AIC-ACC network involved in cognitive effort discount may be useful in discovering biomarkers-related to the neuro-pathophysiology of depression.

Disclosures: I. Park: None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.22/JJ15

Topic: G.05. Mood Disorders

Support: NIMH Grant R01MH113256

Title: Lithium induced increase of regional gray matter over time correlates with improvement of depression score: a 7T high-resolution MRI study

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Abstract: Introduction: Lithium is recognized as one of the most specific and efficacious treatments for bipolar disorder (BD). This study aims to use brain structural imaging acquired from a 7T high-resolution MRI scanner to investigate differences in brain structure during the time of lithium monotherapy between bipolar disorder depression (BDD) and healthy control (HC).

Methods Subjects: This ongoing study has recruited BDD subjects ages 18-60 years from the outpatient psychiatry clinics at Cleveland Clinic and Brigham and Women's Hospital who were on stable medications for 12 weeks. Scans were done at baseline and after 2, and 8 weeks of lithium monotherapy. Closely matched HCs who were imaged at the same time points but did not receive any treatment. The final analyses included 36 subjects: 26 BDD and 10 HC. Imaging: Subjects were scanned on a Siemens 7T Terra MRI scanner. We used T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) imaging. In the preprocessing, the regional gray matter volumes were calculated using a longitudinal design and via a voxel-based morphometry (VBM) approach. Analysis: We conducted second-level linear mixed-effects analysis with segmented and normalized gray matter images in AFNI to calculate the interaction effect of group (BDD vs. HC) x time (baseline, week 2, and week 8). The interaction effect of group x time was examined at cluster-wise corrected significance of $p < .05$ and voxel-wise threshold $p < .001$ (uncorrected).
Results: There were significant interaction effects for group x time in the right and left insular cortex, the right temporal cortex, and the right anterior cingulate cortex. These regions showed regional gray matter volume reduction at baseline in BDD compared to other time points and/or HC. After week 2, these volumes in BDD increased and the increase was maintained through week 8. The increase of regional volume was positively correlated with the improvement of depression score from baseline to week 8.
Conclusions: The investigation of volumetric changes with VBM techniques applied to structural MRI data during the lithium treatment of BD may provide a method for developing biomarkers of the lithium effect and distinguishing between BDD and HC at baseline.
Disclosure: Supported by NIMH grant R01MH113256.

Disclosures: J. Cha: None. **A. Anand:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.23/JJ16

Topic: H.01. Attention

Title: Effects of trait anxiety on the relationship between task difficulty and MMN: Cognitive load condition

Authors: *T. TERUNUMA[1], T. URAKAWA[2], Y. AKIZUKI[1], S. SAITO[1], M. SUZUKI[1], H. GOTO[1], T. OKAZAKI[2], O. ARAKI[1];
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Abstract: The mismatch negativity (MMN) in ERP induced by task-irrelevant auditory stimuli is sometimes measured as a probe method to assess attentional resources. This is because MMN is thought to reflect residual attentional resources and it is expected to decrease when much attention is paid to a main task. However, consistent results have not been reported in previous

experiments. According to the Attentional Control Theory (ACT), task-irrelevant stimulus-induced attention is more difficult to be inhibited by top-down processing in individuals with higher Trait Anxiety (TA) (Eysenck et al., 2007). Therefore, we focused on a possibility that the MMN amplitude may increase conversely in such individuals. Psychological experiments using a perceptual load task reported a correlation between increased TA and prolonged reaction time (RT), but no correlation was observed with accuracy; indicating a decline in processing efficiency (Sadeh et al., 2011). From ACT (Eysenck et al., 2007), task performance in individuals with high TA would be preserved by induction of additional neural processing (compensatory process). However, once task difficulty increases and reaches a certain level, the performance is expected to deteriorate. Therefore, it is possible that accuracy of individuals with high TA may decrease under cognitive load tasks due to the influence of TA on accuracy.
The purpose of this study is to clarify the correlation between TA and behavioral measures (RT, accuracy) and between TA and the amplitude of MMN in response to task-irrelevant stimuli in cognitive load tasks with some difficulty levels. The N-back task was employed as a cognitive load task, and 15 participants performed the task at three levels of difficulty: N = 0, 1, and 2. To measure MMN, task-irrelevant stimuli were oddball sound stimuli (the frequency is 1000 Hz or 1300 Hz and the duration is 50 ms). The results of a two-way repeated measures analysis of variance for behavioral measures showed a decrease in accuracy ($F(1, 14) = 5.465$, $p < 0.05$) and an increase in RT ($F(1, 14) = 91.362$, $p < 0.001$) as the task difficulty increased. Pearson correlation analysis revealed no significant correlations between the behavioral measures and TA in any difficulty levels. However, when the frequency of sound stimuli is 1300Hz, a significant negative correlation ($r = -0.566$, $p < 0.05$) between the difference in TA and MMN amplitude between the 2-back and 1-back condition was observed. This means that individuals with higher TA exhibit more enhancements in MMN amplitude (absolute value) as the task difficulty increases under this condition.

Disclosures: **T. terunuma:** None. **T. Urakawa:** A. Employment/Salary (full or part-time):; Mazda Motor Corporation. **Y. Akizuki:** None. **S. Saito:** None. **M. Suzuki:** None. **H. Goto:** None. **T. Okazaki:** A. Employment/Salary (full or part-time):; Mazda Motor Corporation. **O. Araki:** A. Employment/Salary (full or part-time):; Tokyo University of Science.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.24/JJ17

Topic: H.10. Human Learning and Cognition

Support: NINDS Intramural Competitive Fellowship
ATIP-AVENIR

Title: The brain maintains an active memory of the previous error during motor learning

Authors: *R. QUENTIN[1], F. IWANE[2], E. BUCH[3], D. TODOROV[5], J.-R. KING[6], L. M. CLAUDINO[4], M. VERNET[7], L. G. COHEN[8];
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Abstract: We continuously learn from our past errors in everyday life. Computational models of motor learning have proposed that the brain compensate for a fraction of the previous error on each trial. However, a memory of previous errors has not been observed yet in neural recordings. We recorded magnetoencephalographic (MEG) activity in twenty healthy volunteers while they performed a visuomotor adaptation learning task with different types of perturbation schedules. Using multivariate pattern analyses (MVPA), we demonstrate that the brain encodes and maintains an active neural representation of the previous error several seconds after its perception while learning. Such memory of error is encoded in a distributed neuronal network including prefrontal brain regions. This neural signal is diminished in unstable environment when the previous error is not useful. On the contrary, we did not find any evidence of an active maintenance of a memory of previous action or previous visual feedback. Our results constitute neural evidence of an adaptive memory of error during motor learning.

Disclosures: R. Quentin: None. **F. Iwane:** None. **E. Buch:** None. **D. Todorov:** None. **J. King:** None. **L.M. Claudino:** None. **M. Vernet:** None. **L.G. Cohen:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.25/JJ18

Topic: H.10. Human Learning and Cognition

Support: ISCIII PI19/00298

Title: Shared Neural Pathways of Motor and Cognitive Automatic Behaviors

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Abstract: The extent to which motor and cognitive automatic behaviors share common neural mechanisms is unclear. Unraveling the behavioural and neural mechanisms behind motor and cognitive automatic behaviors holds promise for advancing our fundamental knowledge on organized behaviour and disorders with imbalanced automated processes, such as Parkinson's disease or addictions. This study aims to investigate the behavioural and neural substrates of motor and cognitive automatic behaviors using functional magnetic resonance imaging (fMRI) to determine similar or distinct neural pathways. To address this question, we conducted an fMRI

study involving healthy participants engaged in motor and cognitive automatic tasks. The motor task involved a well-practiced motor activity, such as word handwriting using a gradient from the most automatic (e.g., subject signature) to more goal-directed conditions (e.g., greek words). The cognitive task focused on implicit cognitive associations, using implicit bias towards four possible conditions: two congruent and two incongruent associated to familiar and unfamiliar associations towards names of people in Go/no-Go Association task (GNAT). Tasks were developed to mimic habitual and goal directed processes with varying weight over motor vs cognitive operations. Preliminary findings indicate shared and distinct neural activation patterns in motor and cognitive automatic behaviors. When focusing on striatum, in the motor task, bilateral posterior putamen activity was enhanced during habitual conditions, while increased activity was seen in the anterior putamen and caudate nucleus during goal-directed conditions. Cognitive automatic task showed enhanced posterior ipsilateral putamen in congruent/habitual trials and bilateral caudate nucleus for incongruent/goal-directed trials. Additionally, we found the posterior right putamen as a joint hub for both motor and cognitive automaticity. Our results suggest possible overlapping mechanisms when automatic behaviour is required in humans, involving the right posterior putamen as a converging neural substrate for both types of automatic behaviors.

Disclosures: I. Obeso: None. **P. Guida:** None. **M. Michiels:** None.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.26/JJ19

Topic: H.01. Attention

Title: Effects of trait anxiety on the relationship between task difficulty and MMN: Perceptual load condition

Authors: *Y. AKIZUKI[1], T. URAKAWA[2], T. TERUNUMA[1], S. SAITO[1], H. GOTO[1], M. SUZUKI[1], T. OKAZAKI[2], O. ARAKI[1];
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Abstract: According to the attentional control theory, it is difficult for individuals with higher trait-anxiety to suppress information processing on a task-irrelevant stimulus while performing a difficult task. Although processing efficiency in the brain has been estimated by behavioral data such as an increase of reaction time (less processing efficiency) so far, every aspect of processing efficiency would not be observed in behaviors. We aim to capture the impairment of suppression of task-irrelevant responses by measuring an amplitude of MMN (Mismatch Negativity) that reflects preattentive change-detection in auditory stimuli. According to the perceptual load theory (Lavie et al., 1994), the higher the perceptual load becomes, the more attentional resources allocated to a task-irrelevant stimulus reduces. Therefore, the amplitude of MMN evoked by a task-irrelevant stimulus will decrease as the perceptual load of a task increases.

Although there are some studies that attempted to confirm this hypothesis, the results were not consistent. We assumed that this was due to the difference of individual trait anxiety, which is expected to affect the allocation of attentional resources. We expect that the amplitude of MMN would conversely increase in people with high trait anxiety when perceptual load is high because the task-irrelevant stimuli cannot be ignored.
The purpose of the present study is to clarify how the amplitude of MMN and the behavioral performance correlate with the level of perceptual load and individual trait anxiety.
We set up three levels of perceptual load as the main task, with the oddball paradigm as a task-irrelevant auditory stimulus, which evoked MMN. Participants (N=20) were instructed to detect a target letter (X or N) as soon as possible in the circle of letters consisting of 1, 3, or 6 letters (Load 1, 3, or 6).
As a result, MMN's amplitude increased significantly as the trait anxiety increased when the level of perceptual load increased from load 3 to 6 (r = -0.720, $p < 0.05$). This result indicated that MMN's amplitude decreased for low-anxious individuals, but on the contrary increased for high-anxious individuals. This is consistent with our prediction that MMN's amplitude is subject to not only the levels of perceptual load but also the trait anxiety. On the other hand, there is no significant correlation between behavioral performance and trait anxiety. This result suggests that the MMN enables us to estimate processing efficiency that is not represented in behavioral data. Furthermore, it is thought that the estimate of attentional resources using MMN for low-anxious individuals is effective.

Disclosures: **Y. Akizuki:** None. **T. Urakawa:** A. Employment/Salary (full or part-time):; Mazda Motor Corporation. **T. terunuma:** None. **S. Saito:** None. **H. Goto:** None. **M. Suzuki:** None. **T. Okazaki:** A. Employment/Salary (full or part-time):; Mazda Motor Corporation. **O. Araki:** A. Employment/Salary (full or part-time):; Tokyo University of Science.

Poster

PSTR099. Human Imaging and Behavioral Studies: Depression and Anxiety

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR099.27/JJ20

Topic: H.01. Attention

Title: Task-irrelevant auditory tuning affects perceptual formation under selective attention

Authors: *N. ONO, Y. KURITA, H. GOTO, O. ARAKI;
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Abstract: In a situation where multiple sensory stimuli coexist, it has been shown that attention enhances neural activity associated with the response to the selected stimulus (Hillyard et al., 1973). In previous studies on selective attention, neural processing of attended and unattended stimuli has been independently examined. On the other hand, a critical distinction is made between tuned stimuli, in which all sound components are integer multiples of the fundamental frequency, and mistuned stimuli, in which one partial is not tuned. Mistuned stimuli are readily

identified as distinct auditory stimuli (Darwin et al., 1998). Although the harmonicity of the sounds may influence perception, it is usually difficult to analyze such subtle perceptual changes. In response to an infrequent tone after frequently repeated ones, the mismatch negativity (MMN) component in event related potentials (ERPs) is known to be elicited (Näätänen et al., 1978). It is noted that the perceptual formation process during the repeated standard stimuli contributes to generation of MMN (Sussman, 2007). We think that changes in perception associated with the relationship between multiple auditory stimuli can be captured by measuring MMN. The aim of this study is to clarify whether the MMN in response to deviations of task-relevant stimuli, that reflects perceptual formation is modulated by tuned/mistuned relationships between task-relevant and task-irrelevant auditory stimuli. The experimental procedure is as follows. Task-relevant oddball stimuli and task-irrelevant distractor stimuli were presented simultaneously with a constant interstimulus interval. There were three conditions: (1) tuned (mistuned to tuned deviation) condition, (2) mistuned (tuned to mistuned deviation) condition, and each (3) control (mistuned to mistuned deviation). Participants (23 males, mean age 22.0) were required to report deviant stimuli in the oddball paradigm as soon as possible. The results showed that the MMN amplitude was significantly larger for the tuned condition than control ($p < 0.05$). In contrast, the MMN amplitude was significantly lower for the mistuned condition than control ($p < 0.05$). Therefore, the MMN amplitude elicited by the task-relevant deviant stimulus was influenced by the tuning relation with the task-irrelevant stimuli. These results suggest that the auditory perception augmentedly responds to tuned sound as salient stimuli while it suppresses or disregards mistuned sound. Furthermore, these support that the sound harmonicity affects perceptual formation under selective attention.

Disclosures: **N. Ono:** None. **Y. Kurita:** None. **H. Goto:** None. **O. Araki:** A. Employment/Salary (full or part-time):; Tokyo University of Science.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.01/JJ21

Topic: G.05. Mood Disorders

Support: University of Connecticut Research Foundation
University of Connecticut Holster Scholar Program

Title: Evaluation of Different Classes of Monoamine Uptake Inhibitors: Effects on Effort-based Choice

Authors: *G. EDELSTEIN[1], A. ECEVITOGLU[1], A. GOLDHAMMER[1], S. PAPANIKOLAOU[1], E. LINZ[1], K. BEARD[1], R. OLIVARES GARCIA[2], A. MARTINEZ VERDU[2], M. CORREA[2], J. SALAMONE[1];
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Abstract: Monoamine uptake inhibitors are the most common treatments for depression, but across various drugs there are many different profiles of action on distinct monoamine transport proteins. Although inhibitors of serotonin transport (SERT) are the most widely prescribed antidepressants, evidence indicates that these drugs are limited in their effectiveness at treating motivational dysfunctions such as anergia and fatigue. In contrast, drugs that act on the catecholamines dopamine (DA) and norepinephrine (NE), such as bupropion, are reported to be more effective at treating motivational dysfunction. Rodent tests of effort-based choice are used as models for assessing the effort-related motivational effects of drugs, including antidepressants. The present studies assessed the ability of various drugs that inhibit DA transport (DAT), NE transport (NET), and SERT for their ability to reverse the low-effort bias induced by the VMAT-2 inhibitor and DA depleting agent tetrabenazine (TBZ). In rats tested on the fixed ratio (FR) 5/chow feeding choice task, TBZ shifts choice, reducing lever pressing but increasing chow intake. Previous research showed that the selective DAT inhibitor GBR12909 and the DAT/NET inhibitor bupropion were able to reverse the effort-related effects of TBZ. Furthermore, atypical DAT inhibitors such as modafinil and its analogs can effectively reverse these behavioral effects of TBZ. Recently, the atypical DAT inhibitor MK-26 was reported to significantly reverse the behavioral effects of TBZ (Kouhnavardi, Ecevitoglu et al. Biomolecules, 2022). In the present studies, both the selective NET inhibitor atomoxetine and the NET/SERT inhibitor duloxetine failed to reverse the effort-related effects of TBZ, and in fact tended to further suppress lever pressing. At moderate doses, the NET/DAT inhibitor nomifensine was able to partially reverse the suppression of high-effort lever pressing induced by TBZ. Current antidepressant development efforts include the evaluation of triple uptake inhibitors (TRIs). TRIs exert their effects by inhibiting DAT, NET and SERT. It is hypothesized that TRIs could have motivational effects because of their actions on all three monoamines. In current studies, the TRI diclofensine is being tested for its ability to attenuate TBZ-induced shifts in behavior on the FR5 chow feeding choice task. Additionally, microdialysis methods are being used to assess the neurochemical effects of these different monoamine uptake inhibitors. Taken together with previous studies, the present results suggest that actions on DAT are critical for exerting pro-motivational effects in models of effort-based choice.

Disclosures: G. Edelstein: None. **A. Ecevitoglu:** None. **A. Goldhammer:** None. **S. Papanikolaou:** None. **E. Linz:** None. **K. Beard:** None. **R. Olivares Garcia:** None. **A. Martinez Verdu:** None. **M. Correa:** None. **J. Salamone:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.02/JJ22

Topic: G.05. Mood Disorders

Support: PROMETEO/2020/032
PID2021-125977OB-100

Title: Influence of type of reinforcer and dopamine depletion on sex differences in effort-based decision-making in rats.

Authors: *M. CORREA[1], C. CARRATALA-ROS[1], A. ECEVITOGLU[5], R. OLIVARES-GARCÍA[2], P. MATAS-NAVARRO[3], A. MARTÍNEZ VERDÚ[4], G. EDELSTEIN[5], J. D. SALAMONE[5];
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Abstract: Dopamine (DA) plays an important role in regulating activational and effort-related aspects of motivation. DA receptor antagonists and DA-depletion produce a low-effort bias in rats, shifting choice behavior from high-effort to low-effort alternatives. These tasks also have been used for animal models of motivational symptoms in psychiatric disorders. However, a limitation of these studies is that the vast majority were done in male rodents. Thus, in the present work we characterize the potential sex differences in operant tasks requiring effort-based decision-making. We employed fixed ratio requirements (FR1 and FR5) as well as the concurrent FR5/choice task in male and female adult Sprague Dawley rats. Animals have to lever press for the more preferred reinforcer but they concurrently have a less preferred but free one. In different experiments we used different reinforcers; high carbohydrate pellets vs standard chow food or high sucrose concentration 5% vs low concentration 0.3%. Additional studies investigated the effects of IP injection of the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ), which blocks vesicular DA storage. TBZ was selected because this drug produces depressive symptoms and motivational dysfunctions in humans, and animal studies use TBZ to model these dysfunctions. Under baseline conditions, males typically lever pressed more than females for food, although both sexes consume the same amount of total food since females compensate by consuming more of the free available pellets. However, both sexes had the same level of performance for sucrose, although females had more bouts of the concurrent free sucrose solution. Both sexes had also the same level of preference and consumption of both solutions under free access conditions. TBZ (1 mg/kg) produced a suppression of lever pressing for sucrose only among males. Females were more active on a running wheel, suggesting that they are not more sedentary in general. Investigating sex differences in the pharmacology and neurochemistry of effort-based choice may lead to a greater understanding of the role of sex in motivational dysfunctions in humans.

Disclosures: M. Correa: None. **C. Carratala-Ros:** None. **A. Ecevitoglu:** None. **R. Olivares-García:** None. **P. Matas-Navarro:** None. **A. Martínez Verdú:** None. **G. Edelstein:** None. **J.D. Salamone:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

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Program #/Poster #: PSTR100.03/JJ23

Topic: G.05. Mood Disorders

Support: Ministerio de Ciencia e Innovación Grant PID2021-125977OB-I00
Conselleria d'Innovació, Universitats, Ciència i Societat Digital. Generalitat Valenciana Grant PROMETEO/2020/032

Title: Comparison between male and female mice of different ages on effort-based decision_making procedures: studies of dopamine depletion and CDNF

Authors: *P. MATAS NAVARRO[1], C. CARRATALÁ-ROS[1], R. OLIVARES-GARCÍA[1], A. MARTÍNEZ-VERDÚ[1], J. D. SALAMONE[2], M. CORREA[1];
[1]Univ. Jaume I, Castellón de la Plana, Spain; [2]Univ. of Connecticut, Storrs, CT

Abstract: Comparison between male and female mice of different ages on effort-based decision-making procedures: studies of dopamine depletion and CDNF.
Mesolimbic dopamine (DA) regulates vigor in motivated behavior. These results have been obtained mainly in male rodents. Thus, we compared CD1 male and female mice in effort-based decision-making tests of motivation. These tests offer choices between several reinforcers that require different levels of effort (PROG/choice task and 3-choice-T-maze task). Sweet reinforcers were used in both tasks. In the operant tasks, females worked harder as the task required more effort to access a 10% sucrose solution. Although males and females do not differ in preference for 10% vs 3% solutions under free concurrent presentation, females consume more 10% solutions. The operant task requires a long period of training and changes in the DA system due to age can be mediating this progression in effort. Thus, age and sex factors were evaluated in the T-maze; a short-training requiring task. Both sexes and ages were equally active when habituated to the RW, but females consumed more sweet pellets than males, especially at an older age. Both sexes had a strong preference for the RW compared to more sedentary reinforcers in the 3-choice-T-maze test, but older animals spent less time running and ate more than the young ones showing an anergic pattern. DA depletion reduced time running in older mice but not in adolescents. The cerebral-dopamine-neurotrophic-factor (CDNF) was reduced in older mice of both sexes compared to adolescent mice. These results remark the importance of taking into account differences in sex and age when evaluating willingness to exert effort for specific reinforcers.
Keywords: sex, age, effort, vigor, dopamine, neurotrophic factors, operant, running wheel, mice.

Disclosures: P. Matas Navarro: None. **C. Carratalá-Ros:** None. **R. Olivares-García:** None. **A. Martínez-Verdú:** None. **J.D. Salamone:** None. **M. Correa:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.04/JJ24

Topic: G.05. Mood Disorders

Support: Technology Development Fund 2220781-601

Title: Monoamine disregulation and cell count in a adgrl3.1 mutant model of ADHD

Authors: *K. KARLSSON[1], D. Þ. HALLDÓRSDÓTTIR[2], H. S. SVEINSDOTTIR[2], B. B. SIGURÐSSON[3], H. ÞORSTEINSSON[2];
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Abstract: ADHD is a highly prevalent neurodevelopmental disorder. ADHD is a disorder of frontal neural circuits and enhanced noradrenaline, serotonin and dopamine transmission therein represents the major target of the current therapeutics. Recently we developed a adgrl3.1 zebrafish model of ADHD that was subsequently used for a drug discovery program. In the current project our aim was to further characterize the adgrl3.1 model. First, using mass spectrometry the catecholamine contents was measured and contrasted between mutant and wild-type strains, and second the difference in noradrenaline, serotonin and dopamine neurons between genotypes was quantified. The results confirm a monoamine dysregulation in the mutant line and but reveal no differences in the cell count. The results further validate the disease model, and suggest a functional as opposed to structural neural cause of the disorder symptoms.

Disclosures: K. Karlsson: None. **D.Þ. Halldórsdóttir:** None. **H.S. Sveinsdottir:** None. **B.B. Sigurðsson:** None. **H. Þorsteinsson:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.05/JJ25

Topic: G.05. Mood Disorders

Support: University of Connecticut Research Foundation

Title: Exploring Sex Differences in the Neurochemical and Effort-related Motivational Effects of the VMAT-2 Inhibitor and Dopamine Depleting Agent Tetrabenazine

Authors: *J. D. SALAMONE[1], A. ECEVITOGLU[1], K. R. BEARD[1], S. SRYNATH[1], G. A. EDELSTEIN[1], N. MEKA[1], A. MARTINEZ-VERDU[1,2], R. OLIVARES-GARCIA[1,2], M. CORREA[2];
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Abstract: Dopamine (DA) plays an important role in regulating activational and effort-related aspects of motivation. Extensive evidence shows that DA antagonism, neurotoxic depletion of accumbens DA, and the DA-depleting agent tetrabenazine (TBZ), produce a low-effort bias in rats and mice, shifting choice behavior from high-effort to low-effort alternatives. These tasks

also have been used for animal models of motivational symptoms in psychiatric disorders. However, a limitation of these studies is that the vast majority were done in male rodents. Additional research is needed to characterize the effort-related effects of DAergic drugs in females as well as males. The present studies investigated the neurochemical and behavioral effects of IP injections of the vesicular monoamine transport (VMAT-2) inhibitor TBZ, which blocks vesicular storage) in both male and female rats. TBZ was selected because this drug produces depressive symptoms and motivational dysfunctions in humans, and animal studies use TBZ to model these dysfunctions. This research was conducted employing the concurrent fixed ratio 5 (FR5)/chow feeding choice task. Under baseline or control conditions, male rats typically lever pressed more than females. In the first study with TBZ (0.25-1.0 mg/kg IP), there was a robust dose x sex interaction. TBZ produced a dose-related suppression of lever pressing and an increase in chow intake in male rats, but in this dose range it was ineffective in females. In a second experiment, a 2.0 mg/kg dose was shown to induce a low-effort bias, decreasing lever pressing and increasing chow intake, in both males and females. Across both studies, lever pressing in males was more affected by TBZ than in females. Co-administration of the DA transport inhibitor methylphenidate reversed the effects of TBZ in males injected with 1.0 mg/kg and females injected with the 2.0 mg/kg dose. In order to assess the neurochemical effects of TBZ in male and female rats, parallel studies were conducted to determine the sex-related effects of TBZ administration (Vehicle, 1.0 and 2.0 mg/kg IP) on expression of cFos in nucleus accumbens and neostriatum. There were substantial sex differences in the effect of TBZ on cFos expression in the accumbens. Compared to vehicle, male rats showed a significant increase in the number of cFos positive cells in nucleus accumbens at 1.0 mg/kg TBZ, while females showed an effect at 2.0 mg/kg. Investigating sex differences in the pharmacology and neurochemistry of effort-based choice may lead to a greater understanding of the role of sex in motivational dysfunctions in humans.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.06/KK1

Topic: G.05. Mood Disorders

Support: Camden Health Research Initiative
CMSRU Biomedical Sciences

Title: Antidepressant treatment alters cell type-specific gene expression pathways related to plasticity in mouse hippocampus

Authors: *T. N. FERRARO[1], B. C. REINER[2], S. N. CHEHIMI[2], G. A. DOYLE[2], A. E. WELLER[2], A. I. BATTERMAN[1], D. P. NGUYEN[1], A. WILLIAMS[3], T. M. KECK[3], W. H. BERRETTINI[2], R. J. BUONO[1], R. C. CRIST[2];
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Abstract: Therapeutic and adverse effects of treatments for depression and related disorders involve adaptation of cellular processes in the brain; however, underlying molecular mechanisms are ill-defined. Notably, diverse treatment approaches including monoamine reuptake inhibitors, ketamine, and electroconvulsive therapy are all potentially effective, but it is unknown whether there are common underlying mechanisms of action. To address this question, we treated male C57BL/6J mice with electroconvulsive shock (ECS, 3 seizures, 15 min apart) or ketamine (10 mg/kg, i.p.) and measured seizure response and locomotor activity, respectively, immediately after treatment. We gave control mice sham ECS or an i.p. saline injection. Mice were 10-12 weeks of age (N=4 per group). We euthanized mice 24 hours following treatment, harvested brain, and obtained punch samples of the hippocampus bilaterally. We conducted single-nucleus RNA sequencing using 10x Genomics methodology, clustered cells and analyzed data with the R-packages Seurat and Libra, identifying differentially expressed genes (DEGs) in specific cell types between experimental and control mice. We analyzed DEGs with functional mapping of genetic association studies (FUMA) and ingenuity pathway analysis (IPA) to identify related clinical phenotypes and cell type-specific processes affected by treatment. Results show that ECS most prominently affected 2 subtypes of excitatory neurons, including Prox1-expressing granule cells, upregulating and downregulating hundreds of genes in each subtype. Many DEGs encode proteins that are targets of antidepressant and other psychoactive drugs, or that are involved in the pathogenesis of psychiatric disorders. FUMA revealed statistically significant associations with major depressive disorder, schizophrenia and bipolar disorder, among others. Statistically significant functional pathways that emerged from IPA are enriched for cellular phenotypes related to differentiation, motility, synaptic development and signaling. Alteration of steroid synthesis was a major finding from IPA and activation of the superpathway of cholesterol metabolism was the single most statistically significant pathway alteration detected. Gene expression changes in astrocytes document an acute ECS-induced inflammatory response. Future analyses will compare ECS-induced DEGs and pathway alterations to those induced by ketamine and elucidate overlapping and distinct effects. Better understanding of the mechanistic similarities and differences between these treatments will ultimately improve the clinical management of patients with depression.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.07/KK2

Topic: G.05. Mood Disorders

Support: CONACyT scholarship 615627

Title: Mk-801 enhances the antidepressant effect of classical antidepressants drugs in wistar and wistar kyoto rats.

Authors: J. M. CHAN-MONROY[1], *E. M. ESTRADA[1], C. LOPEZ-RUBALCAVA[2]; [1]Neuropsicofarmacología, Inst. Natl. Psiquiatria, Distrito Federal, Mexico; [2]CINVESTAV-IPN, Mexico DF, Mexico

Abstract: Currently, Major Depressive Disorder (MMD) represents one of the most common psychiatric illnesses in the World and is related to high-stress levels. Even though there is a wide variety of pharmacological treatments for MDD, around 50% of patients resist standard treatment. For this reason, the search for alternative therapies focused on different neurotransmission pathways is imperative. The glutamatergic system has been proposed as one of the possible alternatives. Several preclinical and clinical studies have shown that administering glutamatergic antagonists, such as ketamine or MK-801 (non-competitive NMDA receptor antagonists), induces rapid antidepressant effects. However, these drugs can have security problems for the patients, and the relationship between this treatment and stress isn´t evaluated. Therefore, the main goal of this work was to evaluate the antidepressant-like effects of the combination of sub-optimal doses of MK-801 with classical antidepressants such as sertraline (serotonin reuptake inhibitor) or desipramine (noradrenergic antidepressants in two rat strains with different stress sensitivity (Wistar and Wistar Kyoto). Thus, independent groups of Wistar and Wistar-Kyoto (WKY) rats were administrated with suboptimal doses of desipramine plus MK-801 and sertraline plus MK-801. Subsequently, animals were evaluated in the open field and forced swimming tests to analyze the antidepressant-like effects of these pharmacological combinations. Results showed that only in the WKY strain the combination of drugs (MK-801 + DMI and MK-801 + sertraline) had an antidepressant-like effect, decreasing the immobility behavior and increasing the swimming behavior in both cases without modifying locomotor activity in the open field test. This result could indicate that both pharmacological combinations could significantly activate serotoninergic neurotransmission. In the case of sertraline + MK-801, we can observe a synergic effect, while in Desipramine+MK-801, despite that desipramine actives noradrenergic neurotransmission, the stimulation of the serotoninergic system given by MK-801 is dominant. In conclusion, WKY rats are more sensitive to the effects of the pharmacological combinations than Wistar rats, and the serotoninergic system probably mediates this effect in both cases.

Disclosures: J.M. Chan-Monroy: None. **E.M. Estrada:** None. **C. Lopez-Rubalcava:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

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Topic: B.10. Demyelinating Disorders

Support: JSPS Grant 21KK0134
Tsubota Lab support
NEDO STS grant 19STS007

Title: Violet light (360-400nm) modulates the central nervous system to regulate memory and mood

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Abstract: The photo-stimulation of the external environment serves as a visual signal, as well as a non-visual signal through the protein opsin. In mammals, the non-visual photoreceptor opsin5 (also known as OPN5 or neuropsin) is expressed in the retinal ganglion cells RGCs) and hypothalamus. Violet light with a wavelength of 360-400 nm activates OPN5 and regulates the circadian cycle, thermogenesis, and myopia. However, the function of violet light and OPN5 in brain function is unknown. We showed that violet light, as an external stimulus, regulates memory and mood function. Violet light improves memory function in aged mice and simultaneously increases the expression of oligodendrocyte-related genes such as MBP and MAG in the hippocampus. In addition, violet light improves depressive-like behaviors in the social defeat stress model in an OPN5-dependent manner and increases neural activity and oligodendrogenesis in the prefrontal cortex and nucleus accumbens. The neural network analysis using WGA and Opn5cre; Ai14 mice indicates that the signal received by OPN5-positive retinal ganglion cells is transmitted to the habenula brain region. Conclusions: Our findings revealed a novel function for violet light in regulating cognitive function and mood behavior. The well-conserved OPN5 may be a non-visual photoreceptor for sensing the light environment and maintaining brain function throughout the lifespan. Although OPN5-RGCs project to the MHb, the central mechanism sensing VL needs to be further investigated. The role of violet light via OPN5 in underpinning myelination and oligodendrocyte function in influencing cognition and mood behavior opens an interesting new avenue for research and the development of novel therapeutic treatments for neurodegeneration and neuropsychiatry disorders.

Disclosures: **M. Hayano:** A. Employment/Salary (full or part-time):; Keio University. F. Consulting Fees (e.g., advisory boards); Tsubota Lab, KII, ANRI.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.09/KK4

Topic: G.05. Mood Disorders

Support: NIMH 1R21MH133212

Title: Circuit-specific plasticity underlying the antidepressant effects of transcranial magnetic stimulation

Authors: *M. W. GONGWER[1], A. ENOS[1], A. QI[1], S. RUEDA[1], O. WILLIAMS[1], J. RILEY[1], G. WILKE[1], Y. YANG[2], A. LEUCHTER[1], H. LU[3], L. DENARDO[1], S. WILKE[1];
[1]UCLA, Los Angeles, CA; [2]Natl. Inst. on Drug Abuse, Baltimore, MD; [3]Neuroimaging Res. Br., NIDA IRP, Baltimore, MD

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method for clinical brain stimulation. Several rTMS approaches are now FDA-approved to treat refractory depression and have shown great promise for other neurological and psychiatric disorders. High frequency (HF) rTMS and intermittent theta burst (iTBS) are two commonly used protocols, which are postulated to enhance prefrontal cortex excitability. These protocols are typically applied daily over many weeks to treat depression. More recently, accelerated iTBS protocols have generated substantial excitement due to their ability to promote rapid clinical response in depression. However, clinical outcomes following rTMS are highly variable and poor insight into the underlying cellular and circuit mechanisms limits optimization of therapeutic response. Previous mechanistic studies have been limited by a lack of established animal models with strong face validity for how rTMS is delivered clinically. Our lab has acquired the first rodent TMS coil capable of generating focal, suprathreshold stimulation of a cortical subregion in the mouse brain. Here, we use this coil to probe how HF-rTMS and accelerated iTBS protocols, delivered in awake animals, impact prefrontal function in mice exposed to chronic stress. Both chronic and accelerated rTMS protocols can reverse depression-like behavioral deficits associated with chronic stress. Using Morf3 mice for sparse fluorescent labeling of neuronal populations, we find that rTMS treated mice exhibit cell-type specific changes in dendritic spine density. These findings suggest that circuit-specific structural plasticity may underlie rTMS-induced behavioral changes. In ongoing work, we are continuing to use *in vivo* approaches to determine the circuit-level changes underlying the therapeutic utility of rTMS in depression and other disorders.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.10/KK5

Topic: G.05. Mood Disorders

Support: IN220120 from PAPIIT-DGAPA-UNAM

Title: Effect of repetitive transcranial magnetic stimulation on astrocytes in an animal model of depression

Authors: R. ACOSTA-LUNA, M. GÓMEZ-CHAVARRIN, E. IBARRA-CORONADO, *L. VERDUGO-DIAZ;
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Abstract: Introduction. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive technique used as a treatment for resistant depression. Additionally, rTMS can also have effects on astrocytes. The mechanism of action of this treatment is poorly understood. Recent studies suggest that rTMS may alter astrocytic function and reduce inflammation in the brain, which could contribute to its effectiveness in depression treatment. Objetive. The aim was to evaluate the effect of 10 Hz rTMS on depressive and anxious symptoms in the Wistar rat model of depression, as well as to observe if there is an effect on astrocytic reactivity measured through immunostaining of glial fibrillary acidic protein (GFAP). Methods. Twenty days of CUMS induces depressive and anxious symptoms in male adult Wistar rats (n=26). To measure these symptoms forced swimming, sucrose preference test, open field, and elevated plus maze tests were used. rTMS was applied daily for 15 days (10Hz, 10min/day) using an eight-coil. Immunohistochemistry was performed to evaluate astrocytic reactivity and counting astrocytes in the hippocampus. Results. The model induced depressive symptoms, which were observed by anhedonia and more immobility on the swim test. rTMS treatment induced a reduction in these depressive symptoms. We observed an elevated astrocyte density on dentate gyrus, CA1, and CA3, but not on CA2 of animals with rTMS versus sham-stimulated animals. The 10 Hz rTMS used on the animal model of depression had a significant antidepressive effect and astrocytic reactivity on the hippocampus. Conclusion. These results suggest that 10 Hz rTMS exposure on the animal model of depression induces cellular responses of astrocytes and antidepressant effects and could indicate a potential mechanism of action of rTMS.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.11/KK6

Topic: G.05. Mood Disorders

Title: Screening Glutamatergic Ligands in the Chick Social-Separation Stress Test, A Dual-Drug Screening Model of Treatment-Resistant Depression.

Authors: *T. CASTRO, S. WHITE;
Sam Houston State Univ., Huntsville, TX

Abstract: The chick social-separation stress test is a dual-drug screening assay that models an anxiety phase followed by a depression phase. Utilizing this model, we have characterized a stress-vulnerable, treatment-resistant, ketamine-sensitive avian genetic line. Rodent models of anxiety and depression have demonstrated modulation of glutamate receptors can provide anxiolytic and/or antidepressant effects. Utilizing the Black Australorp genetic line, the purpose of this study was to evaluate glutamatergic ligands reported efficacious in rodent models of anxiety or depression. Separate dose-response studies (n=12-18) were conducted for the following drugs: the AMPAR antagonist NBQX 1, 3, and 10 mg, the mGluR 2/3 antagonist LY341495 1, 3, and 10 mg, and the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) 1, 3, and 10 mg. Separate dose-response studies for the norepinephrine α^2 agonist clonidine and the NMDA antagonist ketamine were included as control comparison for anxiolytic and antidepressant effects, respectively. One-day old male Black Australorp chicks were group housed with access to food and water. Testing occurred on days 5-7 post-hatch. Ketamine was administered i.m. and all other drugs were administered i.p. 30 min prior to exposure to a 90-min isolation stressor. Distress vocalizations (DVocs) were recorded as the behavioral measure. Separate one-way ANOVAs was conducted for each phase of the test to determine drug effects and post-hoc analysis using Fisher's LSD was used to determine specific group differences. Clonidine 0.20mg significantly reduced DVoc rates in the first 5 min of isolation (i.e., anxiolytic effect) but had no effect on DVoc rates during the depression phase (31-90 min). Ketamine 10 mg had no effect on DVoc rates during the anxiety phase (0-5 min) but significantly elevated DVoc rates during the depression phase (31-90 min, i.e., antidepressant effect). NBQX doses of 3 and 10 mg significantly reduced DVoc rates during the first five min of isolation (i.e., anxiolytic effect) but had no effect on the DVoc rates during the depression phase of the test (31-90 min). The mGluR 2/3 antagonist LY341495 and (2R,6R)-HNK had no effect in the anxiety phase of the test (0-5 min) and contrary to our predictions LY341495 and (2R,6R)-HNK had no effect on the depression phase (31-90 min) of the test (i.e., failed to produce antidepressant effects). Our study suggests that antagonism of iGlu AMPARs may be clinically useful in the treatment of anxiety, specifically panic disorder. As the Black Australorp genetic line simulates treatment-resistant depression, LY341495 and (2R,6R)-HNK may not prove useful for this clinical population.

Disclosures: **T. Castro:** None. **S. White:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

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Program #/Poster #: PSTR100.12/KK7

Topic: G.05. Mood Disorders

Support: NIEHS P30ES029067
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Allen Endowed Chair in Nutrition & Chronic Disease Prevention

Title: Antidepressant effects of selective aryl hydrocarbon receptor modulators (SAhRMs) across sex, age, and diet

Authors: R. A. DEBLER[1], P. GALLEGOS[1], A. M. PERTTULA[1], S. SAFE[2], R. S. CHAPKIN[3], *S. EITAN[1];
[1]Psychological and Brain Sci., [2]Vet. Physiol. and Pharmacol., [3]Nutr., Texas A&M Univ., College Station, TX

Abstract: Major Depressive Disorder (MDD) is a severe and debilitating disorder that affects approximately 280 million people worldwide. Unfortunately, the majority of patients have to try several medications or other non-pharmaceutical treatment, around 60% of them respond with only about a 50% reduction in their symptoms, and about one-third do not respond to any treatment at all. Notably, obese individuals are more likely to suffer from depression and are also more likely to be resistant to current medications; 55% of adults who were taking antidepressant medication, but still reported moderate to severe depressive symptoms, were obese. Thus, there is still a critical need for additional choices for medications as well as improving our understanding of the etiology of depression. Our recent studies demonstrated that selective aryl hydrocarbon receptor modulators (SAhRMs) can act as an antidepressant in young adult non-obese female mice (7-8 weeks old). In contrast, although SAhRMs demonstrated a potential to mitigate certain stress effects, it did not appear to be a potential antidepressant in young adult non-obese males. Thus, this study examined the effect of 1,4-dihydroxy-2-naphthoic acid (DHNA), an AhR-active gut bacterial-derived metabolite, in obese female and male mice. Obesity was established by feeding mice for 9-10 weeks with a high fat diet (HFD). Given that obese mice were approximately 13-14 weeks old when ligand administration and behavioral testing began; this study also included a small group of age-matched mice fed with standard laboratory chow diet. We employed the unpredictable chronic mild stress (UCMS) paradigm, which has high translational potential to human depression. Depression-like state was evaluated by scoring the immobility in the forced swim test (FST) as an indicator for despair, and by scoring groom time in the splash test and the tape groom test, which are associated with levels of self-care and motivational behavior. UCMS increased FST immobility time, and reduced splash and groom time in both HFD and chow-fed mice. Importantly, DHNA effectively inhibits these effects of UCMS in both HFD and chow-fed female and male mice. These results indicate that SAhRMs could potentially be effective antidepressants in both young adults and adult females, including non-obese and obese. Remarkably, although appearing to be non-effective in young adult males, SAhRMs could potentially be effective antidepressants in adult males, including non-obese and obese. Further studies should examine the underlying mechanisms for these effects, in order to fully understand the therapeutic potential of SAhRMs, and to reveal the role of the AhR in depression.

Disclosures: **R.A. Debler:** A. Employment/Salary (full or part-time):; Texas A&M University. **P. Gallegos:** None. **A.M. Perttula:** None. **S. Safe:** A. Employment/Salary (full or part-time):; Texas A&M University. **R.S. Chapkin:** A. Employment/Salary (full or part-time):; Texas A&M University. **S. Eitan:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.13/KK8

Topic: G.05. Mood Disorders

Support: Mitacs Canada
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Title: Fatty acid binding protein-5 acts on CB2R/GPR55 to modulate key signaling pathways controlling depressive and anxiety-related behaviours: Possible involvement of adult neurogenesis

Authors: *T. UZUNESER[1,8,2], M. JONES[2,8], M. SARIKAHYA[2,8], D. GUMMERSON[1,3,4], E. PROUD[2,5], H. WANG[9,10], I. OJIMA[9,10], D. HARDY[6,8], W. J. RUSHLOW[2,8], S. R. LAVIOLETTE[2,8,7];
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Abstract: Adult neurogenesis is the process in which newly formed nerve cells are continuously added to the already existing neural network during adulthood. As increased proliferation of newborn neurons was observed following treatment with different classes of antidepressants, and as chronic stress was shown to heavily disrupt proliferation of newborn neurons, pharmacotherapeutic interventions to improve adult neurogenesis can be a promising approach against neuropsychiatric disorders. The endocannabinoid (eCB) system, which modulates many biological processes, including adult neurogenesis, is an encouraging target for pharmacotherapy against neuropsychiatric conditions. A chaperone protein in the eCB system, fatty acid binding protein-5 (FABP-5), is responsible for the intracellular transport of the eCB ligand anandamide for its degradation by fatty acid amide hydrolase. Previously, we showed that pharmacological inhibition of FABP-5 within the prelimbic cortex of rats induced an anxiolytic behavioral phenotype and an altered neurophysiological activity in a CB2R/GPR55 dependent fashion in rats. Furthermore, we showed that systemic inhibition of FABP-5 restores stress-induced anxiogenesis, anhedonia and depression-like behaviour in rats. Here, we aimed to investigate the molecular effects of FABP-5 inhibition using SBFI-103, a selective inhibitor of FABP-5. Following a 2/3-week long chronic unpredictable stress paradigm, we administered SBFI-103 intraperitoneally for 4 weeks (3 injections per week) to adult Sprague-Dawley rats. Thereafter, we investigated mRNA expression levels and activity of proteins in the eCB system within the limbic regions of the rat brain using RT-qPCR and Western blotting, respectively. Furthermore, we examined relevant neurogenesis markers to explore the proliferation and differentiation of newborn neural cells in the subgranular zone of the dentate gyrus using immunohistochemical staining. Our mRNA expression analysis revealed elevated levels of CB2R and GPR55 by SBFI-103 in the ventral hippocampus of stressed animals, consistent with our behavioural findings.

Furthermore, stress-induced reductions of phosphorylated Erk1-2 and p70S6 kinase, key molecules that modulate emotional behaviour, were restored by SBFI-103, again in the ventral hippocampus. These findings provide critical information on understanding mechanistically how inhibition of FABP-5 ameliorates emotional disturbances. Possible pro-neurogenesis effects of SBFI-103, which are currently under examination, will help us further evaluate the therapeutic potential of FABP-5 inhibition on anxiety disorders and depression.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

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Topic: G.05. Mood Disorders

Support: NSTC-111-2320-B-A49-008
NSTC-111-2320-B-A49-037
NSTC-111-2922-I-A49A-014

Title: The role of deep brain stimulation modulated NMDA receptor-dependent synaptic mechanism in social stress

Authors: *C.-W. LEE[1], M.-C. CHU[2], C.-C. KO[2], Y.-F. KO[2], C.-H. CHANG[2], H.-S. CHANG[3], Y.-F. CHEN[3], H.-C. LIN[4];
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Abstract: Introduction: Social stress often leads to psychiatric disorder such as depression. Clinical studies have indicated that prefrontal cortex (PFC) are impacted in depression. The preclinical study has showed that the synaptic plasticity such as long-term potentiation (LTP) was impaired in PFC. Moreover, the N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic function also impaired in depression. Recent study demonstrated that deep brain stimulation (DBS), a method for local stimulation, modulates neural function and considered a potential therapy for treating depression. Previous studies further demonstrated the effect of DBS is involved in NMDAR-related mechanism, including NMDAR subunit GluN2B and downstream molecular CaMKII. However, whether the DBS treatment could modulate synaptic plasticity of PFC by regulating NMDAR-related mechanism in depression is still unclear. Hence, we applied the DBS to investigate the treatment effect on synaptic plasticity of PFC in depression mice model.**Method:** We applied the chronic social defeat stress (CSDS) be a

depression animal model. The behavior tests were examined the depressive-like behaviors. The synaptic plasticity such as long-term potentiation (LTP) was examine by electrical physiology. The NMDAR-related proteins were analyzed by western blot.**Result:** The CSDS-induced depressive-like behaviors were improved by DBS treatment. The CSDS-induced impaired LTP was ameliorated by DBS treatment. Finally, the phosphorylation of GluN2B and CaMKII were decreased by CSDS; whereas the decreased GluN2B and CaMKII phosphorylation were improved by DBS treatment. **Conclusion:** Present study demonstrated that the impaired LTP in PFC was ameliorated by DBS, and which was regulated by NMDAR-related mechanism

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.15/KK10

Topic: G.05. Mood Disorders

Title: Electrophysiological and behavioral effects of ketamine and medial prefrontal cortex deep brain stimulation in a rodent corticosterone model of major depressive disorder

Authors: *M. BERGOSH[1], S. MEDVIDOVIC[2], N. ZEPEDA[3], L. CROWN[5], J. IPE[7], W. CHOI[4], L. ROMERO[6], T. LAM[6], L. DEBATTISTA[6], E. AMJADI[6], E. HAKOPIAN[8], D. J. LEE[3];
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Abstract: There is promising evidence that major depressive disorder (MDD) can be treated with neuromodulation, such as medial prefrontal (mPFC) deep brain stimulation (DBS), or pharmacology, such as ketamine (KET). Here, we evaluate the behavioral and electrophysiological effects of individual and combined DBS and KET in a corticosterone (CORT) rodent model of MDD. In 42 adult male Sprague-Dawley rats, a stimulating/recording left mPFC electrode was implanted. To create an MDD model, on Post Surgery Days (PSD) 10-30, intraperitoneal CORT (40 mg/kg) (n=34) or saline vehicle (n=8) injections were administered. On PSDs 24-30, subsets of the CORT group received either 1) KET (15 mg/kg IP) and sham DBS (n=9); 2) mPFC DBS (30 min, 130 Hz) and KET vehicle (n=8); 3) KET at the onset of DBS (n=9); or 4) sham DBS and KET vehicle (n=8). mPFC LFPs were recorded after treatment on PSDs 24, 29, and 38. Behavioral tests were performed on PSDs 30-39. There was no difference among groups in the Sucrose Preference, Open Field, Novel Object Recognition, or Elevated Plus tests. However, the untreated group had decreased groom time in the Groom Test (GT) and increased immobility time in the Forced Swim Test (FST), relative to the control group. Groom time was negatively correlated with chronic increases in mPFC high frequency

oscillations (HFOs) in the untreated group compared to the control group. Separately, KET and DBS rescued performance on both the FST and the GT. For the KET alone group, rescue of both behaviors were correlated with acute and chronic reductions in sample entropy. In the DBS alone group, acute reductions in low gamma power, compared to the untreated group, were positively correlated with GT rescue. Combined, KET and DBS rescued the FST but not the GT. This correlated with acutely increased low gamma power comparable to the untreated group. The correlation between HFOs, generated by GABAergic interneurons, and MDD-like behavior supports the etiology theory that chronic excitation by stress hormones like CORT drives excitotoxicity-induced inhibition. While KET is thought to treat MDD by antagonizing these interneurons, we instead found decreased sample entropy (a measure of signal complexity) correlated with rescued behavior. Since this was uncorrelated with mPFC HFOs, it suggests KET therapeutically modulates structures that signal to the mPFC. In contrast, the correlation between acutely decreased low gamma power after DBS and rescued behavior points towards acute neuroprotective inhibition. Interestingly, KET inhibited this decrease in low gamma power after DBS, which correlated with MDD-like grooming behavior, suggesting these treatments work through different mechanisms.

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Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

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Topic: G.05. Mood Disorders

Support: HDRF 203840-01

Title: The insula is necessary for antidepressant effects in a preclinical model of intermittent theta-burst stimulation

Authors: *H. H. ASHER, S. JOHNSON, T. CHOWDHURY, R. ZHANG, R. MIKOFSKY, C. LISTON;
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Abstract: Depression is the leading cause of disability worldwide and many patients do not respond to traditional interventions. Accelerated intermittent theta-burst stimulation (iTBS) of dorsolateral prefrontal cortex (dlPFC) is a recently developed form of transcranial magnetic stimulation that shows robust remission rates in patients with treatment-resistant depression. Despite its dramatic efficacy, the mechanisms of iTBS remain unknown. To explore these mechanisms, we developed an optogenetic model of iTBS in mice, using the left prelimbic cortex (lPL) as a correlate of the dlPFC. iTBS sessions consisted of 50 Hz triplet pulses (5ms

duration, 2mW, 465nm LED) repeated every 200 ms for 2 sec with an 8 sec off period over a 10 min session (1,800 pulses total) followed by a 50 min inter-session interval. Using slice electrophysiology, we verified that our stimulation parameters produced high-fidelity EPSPs in lPL neurons. We then subjected naive mice to 3 days of iTBS (10 sessions/day) and observed a robust antidepressant-like effect in the forced swim test (FST; $p<0.01$ iTBS vs Control). Next, we explored immediate early gene expression changes using whole brain cFos staining and light sheet microscopy. Again, after 3 days of iTBS, we found elevated cFos expression in numerous regions, including the insula. Given evidence that depressed patients show dysregulated insula activity, we probed the behavioral contributions of this region in our preclinical model. To model depressive pathophysiology, we subjected mice to a 7-day chronic stress paradigm before administering 3 days of iTBS treatment. A subset of these mice received selective chemogenetic inhibition of insula during iTBS, which blocked the antidepressant-like effects of iTBS in FST ($p<0.01$, iTBS + insula inhibition vs iTBS; $p<0.01$, iTBS vs Control; $p>0.05$, iTBS+insula inhibition vs Control). Ongoing work is exploring the effects of iTBS on network activity. Using fiber photometry we found that iTBS delivered to lPL produced changes in insula activity that were time-locked to stimulation onset. Intriguingly, we observed that the directionality of these effects was state-dependent. When mice were active, lPL stimulation excited insula neurons. Conversely, when the mice were inactive, lPL stimulation inhibited these neurons. Taken together, our results illustrate behavioral and electrophysiological validity of our preclinical model of accelerated iTBS. They also show that insula activity is necessary for these behavioral effects. In future work, we will explore lPL-insula network dynamics as well as cell-type specific mechanisms underlying lasting iTBS effects.

Disclosures: **H.H. Asher:** None. **S. Johnson:** None. **T. Chowdhury:** None. **R. Zhang:** None. **R. Mikofsky:** None. **C. Liston:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.17/KK13

Topic: G.05. Mood Disorders

Title: Ketamine's effects in adolescent female rats

Authors: *M. FRIAR, M. GOMEZ;
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Abstract: According to estimates, around 17% of adolescents go through at least one episode of major depression before entering adulthood. While there are thirty-two drugs approved for the treatment of depression in adults, the number reduces significantly to only seven approved for minors. Among adolescents receiving treatment for depression, nearly 40% exhibit no improvement in depressive symptoms even after undergoing two treatment interventions. In 2019, the FDA approved the use of ketamine for adult patients with treatment-resistant

depression. However, ketamine has not yet been granted approval for use in adolescents. This study investigated the effectiveness of a single dose of ketamine (0 mg/kg, 5 mg/kg, and 10 mg/kg) in adolescent female Wistar-Kyoto and Wistar rats. The selection of the Wistar-Kyoto (WK) strain was based on their suitability as an animal model for depression, allowing us to study the effects in a context of endogenous depression. Wistar (WIS) rats were chosen as a control group to assess the impact of ketamine on healthy animals. Animals underwent testing starting in their adolescence into early adulthood (postnatal days 35 to 61) at multiple time points (24 hours, 7 days, 14 days, 21 days) following the administration of ketamine. The forced swim, two-bottle sucrose, novel object recognition, light dark, and open field tests were used to assess the behavioral effects of ketamine.
In WK rats, the administration of both doses of ketamine led to a reduction in the duration of immobility during the forced swim test, demonstrating antidepressant effects. In contrast, WIS rats treated with ketamine displayed a prolonged period of immobility compared to the saline group, suggesting depressive behavior. In the novel object recognition test, it was observed that WKY rats treated with ketamine exhibited a greater amount of time spent with the novel object, indicating an improvement in memory. In contrast, the memory of WIS rats was not affected by ketamine. In both WKY and WIS strains, ketamine did not result in any significant changes in anhedonia, as assessed through the two-bottle sucrose test. Furthermore, ketamine did not induce any alterations in anxiety levels, as measured by the open field and light dark tests. In conclusion, the administration of ketamine to WK rats alleviated depression-like symptoms, as indicated by the forced swim test. However, other measures employed in the study did not yield significant responses. In WIS rats, ketamine did not demonstrate any adverse effects as shown in the two-bottle sucrose, novel object recognition, open field, and light dark tests; but induced depressive-like behaviors specifically in the forced swim test.

Disclosures: **M. Friar:** None. **M. Gomez:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.18/KK14

Topic: G.05. Mood Disorders

Title: Differential effects of ketamine in novelty suppressed feeding and novel object recognition tests in Long-Evans rats

Authors: F. ZHANG[1], K. L. NICHOLSON[2], K. L. SHELTON[2], S. LINGINENI[1], C. MAGEE[1], K. RUSSO[3], S. VENKATESAN[1], ***J. H. PORTER**[1];
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Abstract: Acute dosing with ketamine in patients with depression can produce a variety of adverse effects in patients including sedation, psychotomimetic, cognitive disruption, and other side-effects. Clearly, the relationship between ketamine's therapeutic and adverse effects needs

to be better understood. This study examined ketamine's acute antidepressant-like effects in male Long-Evans rats in the Novelty Suppressed Feeding (NSF) test and ketamine's acute effects on cognitive function in the Novel Object Recognition (NOR) test. For NSF testing, food-deprived rats were tested for latency to feed after placement in a novel open field following either vehicle or ketamine administration (10 or 30 mg/kg, 30 min IP). Then after a one-week washout period NOR testing was conducted in a Y-maze. There was a familiarization session (5 min) in which two identical objects were introduced in two of the arms, followed by a 10 min timeout in the home cage. Subsequently, the rats were returned to the maze for a 5 min discrimination session in which the rats' ability to distinguish between familiar and novel objects was assessed. Five minutes before the familiarization session, either vehicle or ketamine (10 or 30 mg/kg, IP) was administered. All behavioral sessions were video recorded and scored for latency to eat (NSF) and time interacting with objects (NOR) by 2-3 scorers who were blind to treatment conditions. In the NSF test, 10 mg/kg dose of ketamine (M = 300.2 sec, SEM = 28.6) significantly decreased the latency to feed (Veh M = 418.6 sec, SEM = 32.8); however, this effect was absent at the 30 mg/kg dose (M = 457.9 sec, SEM = 30.8). For NOR, the 10 mg/kg dose (M = 0.62, SEM = .03) produced no significant effect on proportion of time spent with the novel object (Veh M = 0.66, SEM = .03); whereas, the 30 mg/kg dose significantly decreased the proportion of time spent with the novel object (M = 0.54, SEM = .03). These results demonstrated that only the 10 mg/kg dose of ketamine produced an antidepressant-like effect in NSF, but this dose had no effect on cognition as measured by NOR. The 30 mg/kg dose of ketamine did not produce an antidepressant-like effect in NSF, consistent with other preclinical studies of ketamine's antidepressant-like effects, but did produce a significant disruption in cognition as measured in NOR. Thus, there appears to be a clear separation between ketamine's acute antidepressant-like effects and cognitive effects based on ketamine dose. As part of our ongoing research, the opioid system's potential role in ketamine's antidepressant-like effects and cognitive effects also are being examined in relation to the potential relationship between ketamine dose and treatment time.

Disclosures: F. Zhang: None. **K.L. Nicholson:** None. **K.L. Shelton:** None. **S. Lingineni:** None. **C. Magee:** None. **K. Russo:** None. **S. Venkatesan:** None. **J.H. Porter:** None.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.19/KK15

Topic: G.05. Mood Disorders

Title: In vivo neural circuit imaging reveals functional biomarkers of antidepressant ketamine and guides preclinical efficacy testing

Authors: *O. MILLER, L. BELLIER, S. HUANG, L. GRAY, J. BAIK, J. NASSI;
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Abstract: Despite decades of concerted effort and significant investment, there are few new treatment options for the ~970 million people living with Severe Mental Illness. The current paradigm for evaluating new treatments, primarily semi-anthropomorphic behavioral assessments, is severely underperforming as evidenced by the high rate of late-stage clinical trial failure for lack of efficacy. An alternative approach for efficacy testing is to leverage our understanding of the neural circuitry that is compromised in psychiatric disease to develop preclinical assays that read out the instantaneous relationship between neural activity and behavior. Here we make use of this approach, using Inscopix miniscopes (nVista) and genetically-encoded calcium sensors (GCaMPs), to assess how pharmacological interventions impact neural circuits with relevance to depression. A single, low dose of the NMDA receptor antagonist ketamine produces rapid and durable antidepressant effects in patients with Treatment Resistant Depression. Identifying replicable biomarkers of efficacious antidepressants such as ketamine in rodent models will allow for screening of novel putative antidepressants for preclinical drug development. In this study, we used single cell resolution calcium imaging in awake, behaving mice to uncover biomarkers of stress induced depression, and of ketamine's effects at two temporal scales. First, we looked at timescales coincident with ketamine's rapid antidepressant effect, encompassing the time of maximum brain exposure. In conflict with the "disinhibition hypothesis", we observe multiple functional ensembles with divergent responses to acute ketamine treatment. Furthermore, we observed enhanced coherence of mPFC pyramidal neurons at dissociative, but not at antidepressant dosages. Second, we looked for signatures of ketamine's durable antidepressant effects, three and 24 hours after dosing. We observed changes in depression-related behavior and neural circuit function at both timepoints, providing a neural biomarker of sustained antidepressant effects.
We conducted similar studies to assess the efficacy of the putative antidepressant scopolamine and the failed candidate rapastinel (GLYX-13), and found that their impact on neuronal function significantly diverges from ketamine. These studies are the first of their kind imaging large populations of individual mPFC neurons during active behavior and provide novel signatures of ketamine's effects at antidepressant and dissociative doses. Furthermore the data suggests that functional brain imaging can serve as a predictive tool for efficacy testing of novel drugs in development.

Disclosures: **O. Miller:** A. Employment/Salary (full or part-time):; Inscopix. **L. Bellier:** A. Employment/Salary (full or part-time):; Inscopix. **S. Huang:** A. Employment/Salary (full or part-time):; Inscopix. **L. Gray:** A. Employment/Salary (full or part-time):; Inscopix. **J. Baik:** A. Employment/Salary (full or part-time):; Inscopix. **J. Nassi:** A. Employment/Salary (full or part-time):; Inscopix.

Poster

PSTR100. Animal Models of Mood Disorders: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR100.20/KK16

Topic: G.05. Mood Disorders

Title: The IFN-alpha model of depression and inflammation has highly robust and reproducible behavioural effects and activates the central and peripheral immune system

Authors: M. GLASS[1], R. OGLESBY[1], C. DE PASQUALE[1], A. FREEBURN[1], J. KEALY[1], A. YENNEMADI[2], G. JAMESON[2], J. KEANE[2], G. LEISCHING[2], M. BIANCHI[1];
[1]Ulysses Neurosci. Limited, Dublin, Ireland; [2]TB Immunol. Group, Dept. of Clin. Med., Trinity Translational Med. Inst., Dublin, Ireland

Abstract: Interferon-alpha (IFN-α) is an innate cytokine that is used clinically as a treatment for various cancers and viral infections. IFN-α binds to the IFNAR1 and 2 receptors, initiating signalling of STAT, MAPK/ERK and PI3K pathways, which in turn influence gene expression profiles of affected cells. Up to 48% of patients experience depressive symptoms, which can be reversed with chronic SSRI treatment. We have repeatedly shown that this phenomenon can be back-translated into rats, establishing a neuroinflammatory model of depression. Ketamine, a NMDA antagonist and fast-acting antidepressant, has also consistently reversed IFN-α-induced depression-like effects in this model. Five separate studies have been conducted that have investigated the behavioural effects of ketamine in the IFN-α model. In each of these studies, Wistar rats were treated (3x/week for 3-4 weeks) with IFN-α (170,000IU/kg, SC) to induce a depression-like behavioural phenotype. Depression-like behaviour was assessed with the forced swim test (FST) 24-hours post-administration of ketamine (acute, 5mg/kg, SC). In all these studies, ketamine rescued an IFN-α-induced increase in immobility, showing that this effect is highly reproducible. We combined the data from each individual study to see whether this effect survived with a greater sample size. For each individual study, behavioural scores were normalized to the saline-control group. The normalized scores were analysed using a one-way ANOVA followed by Fisher's LSD. With sample size ranging from 61-66 per group, we found that IFN-α very significantly increased immobility and decreased swimming, emphasizing the robustness of the model. In addition to our previously shown effects on inflammation, neurogenesis, and synaptic plasticity, recent results have shown that this IFN-α-induced depression is associated with concurrent activation of the central and peripheral immune system. Peripherally, using real-time metabolic analysis of the total bone marrow immune cell population, we have found an increase in oxygen consumption rate (OCR) and glycolytic proton efflux rate (GlycoPER) in animals treated with IFN-α. Centrally, we observed a decrease in hippocampal P-Akt expression in the IFN-α treated rats, associated with IFN-α-induced activation of the PI3K pathway. This effect was was rescued by acute ketamine (5 mg/kg, SC). Overall, these results support the reproducibility and reliability of the IFN-α model of inflammation and depression.

Disclosures: M. Glass: None. **R. Oglesby:** None. **C. De Pasquale:** None. **A. Freeburn:** None. **J. Kealy:** None. **A. Yennemadi:** None. **G. Jameson:** None. **J. Keane:** None. **G. Leisching:** None. **M. Bianchi:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.01/KK17

Topic: G.07. Post-Traumatic Stress Disorder

Support: MH131587
MH122414
MH120498
MH120569
MH123742
AG071523
AG079292

Title: Unique protein degradation profiles in the amygdala and anterior cingulate cortex during the formation of a directly vs. indirectly acquired auditory fear memory

Authors: *M. B. PATRICK, S. NAVABPOUR, W. K. RAY, R. HELM, T. J. JAROME; Virginia Polytechnic Inst. and State Univ., Blacksburg, VA

Abstract: Post-traumatic stress disorder (PTSD) is a major anxiety disorder that affects 6% of the world population, with females being 2-3 times more likely than males to develop it. Recent progress has been made in elucidating the brain molecular mechanisms supporting the formation of fear memories that underlie PTSD, with these studies primarily examining individuals that directly experience traumatic events. However, some individuals acquire PTSD from witnessing a traumatic event happen to someone else in close proximity. However, the molecular mechanisms supporting the formation of indirectly acquired fear memories have yet to be explored. Here, we tested whether the molecular signature for directly and indirectly acquired fear was the same, specifically focusing on the amygdala because it has a universal role in fear memory formation, and the anterior cingulate cortex (ACC) as this region has been shown to be critically involved in the formation of memories for indirect fear associations. As a marker of the molecular signature for fear memory formation, we used an unbiased proteomic analysis of K48 polyubiquitination, a marker for protein degradation that we have consistently shown is critical for fear memory formation in several brain regions, including the amygdala. We found that in the amygdala and ACC male and female observer rats had a smaller but largely distinct protein degradation profile from the demonstrator rat that they watched undergo auditory fear conditioning. These data suggest that indirectly and directly acquired fear memories have distinct molecular signatures, which has important implications for developing treatments for "bystander" PTSD.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.02/KK18

Topic: G.07. Post-Traumatic Stress Disorder

Title: Methylone: Distinct Pharmacological and Mechanistic Effects Compared With MDMA

Authors: *J. WARNER-SCHMIDT[1], M. STOGNIEW[1], B. MANDELL[1], S. J. OLMSTEAD[1], B. KELMENDI[2];
[1]Transcend Therapeut., New York, NY; [2]Yale Univ. Sch. of Med., Yale Univ. Sch. of Med., Hamden, CT

Abstract: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric illness affecting 12 million adults in the United States in a given year. Available treatments are limited. SSRIs represent first-line pharmacological options, but the therapeutic response is slow. Most patients do not show significant effects until at least 4-8 weeks of continuous treatment, and even when optimally delivered, 30-40% of patients do not respond at all. MDMA-assisted psychotherapy has shown promise in recent clinical trials and may soon become an available treatment for PTSD. Methylone is the beta-ketone analog of MDMA, but shows shows distinct pharmacological and subjective effects. Initial clinical studies of methylone include two published Phase 1 studies and two retrospective clinical case series reporting that methylone is well-tolerated and may alleviate symptoms of PTSD and MDD and is non-hallucinogenic. Methylone is active in a preclinical model of PTSD, and shows robust, fast-acting, and long-lasting antidepressant-like activity in the Forced Swim Test (FST) as well as anxiolytic activity. An SSRI did not reduce methylone's activity, a notable distinction from MDMA. Here we explore methylone's mechanism of action as it relates to efficacy and safety. Methylone blocked reuptake and facilitated release at monoamine transporters (i.e., SERT, NET, DAT). Results showed that methylone's relative affinities for the different transporters were distinct from MDMA. Specifically, methylone had less effect on serotonin and dopamine transporters. To determine whether these sites of action were specific, the agonist/antagonist activity of methylone (vs. MDMA) was measured using a high throughput beta-arrestin-based screen of 168 different G-protein coupled receptors (GPCRs). Methylone showed no agonist or antagonist activity at any GPCRs while MDMA showed activity at several GPCRs. Previous work has shown that MDMA is a 5HTR2B agonist, which may have cardiovascular safety implications. In contrast, we found that methylone showed no activity at this receptor. Finally, we examined the downstream gene expression changes induced by methylone and MDMA using RNAseq in brain areas relevant to PSTD and MDD. Drug-induced gene expression was compared between methylone and MDMA-treated groups, further highlighting the differences between these structurally similar drugs. Together, this work demonstrates that methylone shares important therapeutic features with MDMA but also has distinct pharmacological and mechanistic properties that may have significant implications for the treatment of PTSD.

Disclosures: **J. Warner-Schmidt:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transcend Therapeutics. **M. Stogniew:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transcend Therapeutics. **B. Mandell:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt

of intellectual property rights/patent holder, excluding diversified mutual funds); Transcend Therapeutics. **S.J. Olmstead:** A. Employment/Salary (full or part-time):; Transcend Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transcend Therapeutics. **B. Kelmendi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transcend Therapeutics. F. Consulting Fees (e.g., advisory boards); Transcend Therapeutics.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Topic: G.07. Post-Traumatic Stress Disorder

Support: K08 MH122733
DOD CDMRP TP220107
BBRF NARSAD
VA National Center for PTSD
Connecticut Division of Mental Health and Addiction Services

Title: Investigating MDMA-induced neural plasticity at subcellular and network levels

Authors: *J. RONDEAU[1], S. JEFFERSON[2], P. WEHRLE[2], A. YU[2], A. P. KAYE[2];
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Abstract: MDMA (3,4-methylenedioxymethamphetamine) has been shown to reduce symptoms of post-traumatic stress disorder (PTSD) when paired with psychotherapy (Phase 3 clinical trial) and enhance fear extinction learning in stressed animals. These findings have fueled speculation that MDMA may be capable of rapidly inducing neural plasticity, thus causing it to be characterized as a psychoplastogen; however, previous studies on MDMA-induced plasticity have been limited to chronic administration of MDMA, often with confounding neurotoxicity, and relatively little is known about the plasticity mechanisms of a single, moderate dose. Here, we investigated MDMA-induced neural plasticity in mice on both a structural (dendrite) and network (whole-brain) level. Two-photon imaging (Thy1-GFP) was used to track dendritic spines in the medial frontal cortex of mice treated with a single dose of MDMA or saline, and cell markers were used to identify cell-type specific populations activated by MDMA across regions. Thus, we map the subcellular and circuit-level plasticity induced by MDMA in order to better understand structural and functional changes relevant to its effect on emotional behaviors.

Disclosures: J. Rondeau: None. **S. Jefferson:** 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.; SRA with Freedom Biosciences, not relevant to current study. **P.**

Wehrle: None. **A. Yu:** None. **A.P. Kaye:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funding from Transcend Therapeutics and Freedom Biosciences (not for current study).

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.04/KK20

Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH/INBRE Grant P20GM103499

Title: Effects of a dopamine D_3 antagonist SB-277011A on the acquisition of post-traumatic stress disorder in male C57 mice

Authors: *C. PETTY[1], B. ETIENNE[2], O. RICE, Sr.[3];
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Abstract: Post-traumatic stress disorder (PTSD) is defined as an anxiety disorder that can develop when an individual experiences or is exposed to a traumatic event. In a recent study in our laboratory, selective dopamine (DA) D3 receptor antagonist SB-277011A assisted in attenuating effects of PTSD in male Sprague-Dawley rats when administered prior to a revised single-prolonged-stress protocol (SPS: forced swim, restraint stress, and random foot shock). Here, we hypothesized that an acquisition period might exist in which the selective DA D3 receptor antagonist SB-277011A (12.5 mg/kg delivered intraperitoneally) administered post-SPS would block the development of PTSD in male C57 mice (n = 40). Tone-induced fear (assessed by measuring hypervigilance and time spent in closed versus open arms of a plus maze) was utilized in our modified SPS model of PTSD. Mice were divided into 4 groups, one which received either SB-277011A or vehicle 1 hour or 48 hours after SPS. Mice treated with vehicle 1 hour (p = 0.041) as well as mice treated with vehicle (p= 0.014) and SB-277011A (p = 0.044) 48 hours after SPS paired with a distinct tone showed a significant increase in freeze times and time spent in the closed arm of the plus maze. Mice treated with a single intraperitoneal injection of 12.5 mg/kg of SB-277011A 1 hour after SPS paired with a distinct tone showed no significant change in freeze times when compared to controls (p = 0.617), indicating that PTSD expression was blocked by the SB-277011A treatment. This was accompanied by a significant decrease in time spent in the closed arm of the plus maze when tested 7 days after exposure to SPS (p = 0.013). These results indicate that there is a 1-hour time window after exposure to SPS in which we can block the development of PTSD as well as anxiety and depression symptoms that are related to PTSD when treated with SB-277011A. In a human model of PTSD, these findings may offer a potential method for persons exposed to a traumatic event to be treated on-site for PTSD to attenuate the negative symptoms that accompany this mental illness.

Disclosures: **C. Petty:** None. **B. Etienne:** None. **O. Rice:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

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Topic: G.07. Post-Traumatic Stress Disorder

Support: NRF-2019M3E5D2A01066259
NRF- 2022R1A2C3013280

Title: Exploration driven by a medial preoptic area to periaqueductal gray circuit facilitates fear extinction in mice

Authors: J. RYOO[1,2], A. SHIN[1], K. SHIN[1], J. LEE[1], D.-G. KIM[1], S.-G. PARK[1], D. KIM[1,2];
[1]Dept. of Biol. Sci., [2]Dept. of Brain and Cognitive Sci., KAIST, Daejeon, Korea, Republic of

Abstract: Exposure therapy, a common treatment for panic and post-traumatic stress disorders (PTSD), relies on repetitive exposure to fear-associated stimuli. This study investigates the role of the medial preoptic area circuit in fear extinction. Activation or inhibition of the circuit did not induce conditioned preference or avoidance of specific zone but influenced motivation for exploring fear-conditioned areas. By repetitively entering the fear-conditioned zone using MPA-vPAG circuit photostimulation, fear extinction was facilitated. These findings reveal a circuit-based mechanism for exposure therapy and provide insights into the formation of extinction memory. Understanding this circuitry can enhance therapeutic strategies and improve patient outcomes.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

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Program #/Poster #: PSTR101.06/LL2

Topic: G.07. Post-Traumatic Stress Disorder

Support: US Army Medical Research and Development Command Military Operations Medical Research Program #19250

Title: Evaluation of dietary changes in Omega-3 polyunsaturated fatty acids on the intestinal microbiome in rodent model of military-relevant traumatic brain insults

Authors: *M. R. RUSLING[1], J. DEMAR[1], A. GAUTAM[1], N. CHAKRABORTY[1], M. PATEL[1,3], A. HOKE[1], D. M. WILDER[2], J. LONG[2], M. JETT-TILTON[1], R. HAMMAMIEH[1]; [2]Blast-Induced Neurotrauma Br., [1]Walter Reed Army Inst. of Res., Silver Springs, MD; [3]ORISE Fellow, Oak Ridge, TN

Abstract: BACKGROUND: When deployed, US soldiers suffer high rates of traumatic brain injury (TBI) and stress, while also undergoing changes in diet. This creates a need to understand how nutrition contributes to the development of sequelae from these exposures. Dietary long chain omega-3 polyunsaturated fatty acids (omega-3s) are crucial components of neuronal membranes, and omega-3 deficiency is a risk factor for neuropsychiatric disorders. The gut's bacterial microbiome (GMB) modulates brain activity through intestine intraluminal metabolism. Thus, we explored if an omega-3 poor diet increases vulnerability to TBI and stress. **METHODS**: Adult male rats (n = 6 / group) were raised for 6 weeks on an omega-3 enriched or poor diet. Anesthetized animals were exposed once to a blast over pressure wave and impact skull concussion, to induce a TBI. Separate rats were subjected once to forced immersion underwater to cause an acute stress reaction. Shams received anesthesia or free swimming. Behavior was examined to 14 days, using motor coordination or "anxiety" tests. Fecal pellets were collected, and the GMB evaluated by 16S rRNA sequencing. Terminal blood was also assayed. **RESULTS**: Our findings in rats showed that TBI and stress caused significant behavioral and blood-chemistry impairments, which were exacerbated by omega-3s deficiency. This was associated with decreases of GMB diversity in shams or after stress, but not for TBI. Diet, however, significantly influenced GMB composition irrespective of the insults, which was distinct from shams; and taxa shifts correlated with behavioral and physiological outcomes. Compositionally, TBI and stress models had many exposure-related effects. Stepwise selection found that *Firmicutes* have a negative association with blood lactate dehydrogenase (LDH) concentrations in both insults. **CONCLUSIONS:** Our results suggest omega-3 deficiency can lower resistance to TBI and stress. GMB status appears integral to this. LDH rises with cellular damage and is inversely correlated with favorable neuropsychiatric outcomes. Finding a GMB to LDH relationship identifies the GMB as a potential therapeutic target for stress and TBI. **DISCLAIMER**: Research was conducted under an institutionally approved animal care and use protocol in compliance with the Animal Welfare Act, and all other Federal requirements. Opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the US Army or DoD.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.07/LL3

Topic: G.07. Post-Traumatic Stress Disorder

Support: Student Touro Research Fellowship Grant Program Award 2022 (log # 017016).

Title: Therapeutic Potential of Acetate Supplementation in Mitigating Traumatic Stress-Induced Impairments in Male Rats

Authors: *A. TANELIAN[1], B. NANKOVA[2], F. HU[2], J. SAHAWNEH[1], E. L. SABBAN[1]; [1]New York Med. Col., Valhalla, NY; [2]New York Med. Col., Brewster, NY

Abstract: Emerging research suggests that the gut microbiota and their metabolites play a significant role in the development of neuropsychiatric disorders. Recently, we demonstrated that rats susceptible to single prolonged stress (SPS), rodent model for post-traumatic stress disorder (PTSD), have an overall pro-inflammatory gut microbiota. Additionally, they had 25% lower cecal acetate levels than SPS-resilient rats, which correlated inversely with anxiety index. Here, we investigated the potential therapeutic role for the microbial metabolite, acetate, in alleviating the adverse effects of traumatic stress. Sprague Dawley male rats were randomly divided into unstressed controls (n=8/group), or groups exposed to SPS (n=14/group). The groups received continued oral supplementation of either 150mM of Na-acetate or Na-chloride in the drinking water. Two weeks after SPS, behavioral analyses were performed using open field (OF), social interaction (SI), elevated plus maze (EPM), and forced swim (FS) tests. After the last behavioral test, animals were sacrificed, and serum and brain (ventral hippocampus) were collected. Urine samples were collected before and 30 mins into the immobilization step of SPS. The behavioral analyses demonstrated that while acetate supplementation did not affect the behavior of the unstressed controls, it mitigated the negative impact of traumatic stress in the SPS-exposed group. This was evident by the improved body weight gain, decreased anxiety-like behavior on the OF and EPM tests, and improved social behavior on the SI test. These behavioral improvements were associated with several mechanistic changes. Acetate supplementation attenuated the SPS-triggered induction of urinary epinephrine levels, suggesting modulation of the stress response. It also induced epigenetic modifications by decreasing the expression of the histone deacetylase (HDAC2) gene in the ventral hippocampus. Additionally, acetate inhibited neuroinflammation by reducing the density of Iba1+ cells and the gene expression of the pro-inflammatory cytokine IL-1ß. Moreover, it led to increased serum β-hydroxybutyrate levels. Overall, our study demonstrates a causal relationship between acetate supplementation and the mitigation of several SPS-induced behavioral impairments. Mechanistically, it impacted neuronal and metabolic pathways including changes in stress response, epigenetic modifications, neuroinflammation and showed novel link to ketone body production. The study demonstrates the therapeutic potential of acetate supplementation to alleviate adverse responses to traumatic stress.

Disclosures: A. Tanelian: None. **B. Nankova:** None. **F. Hu:** None. **J. Sahawneh:** None. **E.L. Sabban:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.08/LL4

Topic: G.07. Post-Traumatic Stress Disorder

Title: Efficacy of fluoxetine and r-ketamine in attenuating conditioned fear in mice

Authors: *M. WELLS[1], A. DONAR[2], A. LACROSSE[2];
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Abstract: This study assesses new potential treatment options for Post-Traumatic Stress Disorder (PTSD). Symptoms of PTSD are debilitating and detrimental to a person's quality of life, effecting their cognition, behavior and mood. PTSD also has high rates of comorbidity with major depressive disorder, obsessive compulsive disorder, and agoraphobia. Current pharmacological treatments for PTSD are inadequate, with only 50% of patients reporting any benefit from treatment. This highlights a need for new treatment options. Ketamine, a dissociative anesthetic, has antidepressant effects and was recently FDA approved for treatment-resistant depression. Fluoxetine (FLX), a selective reuptake inhibitor, also effectively treats depression and anxiety disorders. We seek to determine whether FLX, *R*-ketamine, or a combination of the two will be most effective in reducing the onset of symptoms related to this disorder. Treatment groups included saline, *R*-ketamine, FLX or a combination of *R*-ketamine and FLX. Mice were placed in an operant chamber where they underwent fear conditioning (FC). Mice in the ketamine (10 mg/kg, i.p.) or saline groups received an acute injection four hours after FC. Mice in the FLX (10 mg/kg) group also began treatment 4 hours after FC, but received treatment through their drinking water for two weeks after FC. 24 hours after FC, all mice were placed back into the operant chamber and were presented with the white noise only. They were assessed for freezing behavior, which is indicative of fear memory and a sign of PTSD. Two weeks after FC, mice were again placed into the operant chamber and presented with white noise only and assessed for freezing behavior. 24 hours after, mice were placed into an open-field apparatus and observed for symptoms related to generalized anxiety disorder (GAD). Results indicate that the combined treatment of FLX and *R*-ketamine most improves behaviors associated with PTSD and GAD. Future experiments will include analyzing protein adaptation in brain regions that drive PTSD and GAD. This study will contribute to current research related to the topic of PTSD and determine the efficacy of *R*-ketamine and FLX as a treatment for this disorder.

Disclosures: M. Wells: None. **A. Donar:** None. **A. LaCrosse:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Program #/Poster #: PSTR101.09/LL5

Topic: G.07. Post-Traumatic Stress Disorder

Support: K08 MH122733
va national center for ptsd
DoD CDMRP
Narsad young investigator

Title: Role of norepinephrine in the circuit and behavioral-level characterization of MDMA

Authors: *A. ROSADO[1], A. YU[2], J.-H. YANG[2], J. RONDEAU[2], A. BASU[1], C. J. PITTENGER[2], Y. LI[3], J. FENG[3], A. P. KAYE[2];
[1]Interdepartmental Neurosci. Program, [2]Dept. of Psychiatry, Yale Univ., New Haven, CT; [3]Peking Univ., Beijing, China

Abstract: PTSD is a psychiatric disorder triggered by a traumatic or stressful event. The patients experience severe anxiety, emotional distress, trauma-related avoidance, arousal, and reactivity, and cognition and mood impairments. However, the available treatments, such as psychotherapy and selective serotonin reuptake inhibitors (SSRIs), have a low efficacy. 3,4-Methylenedioxymethamphetamine (MDMA) demonstrated substantial reduction of PTSD symptoms in Phase 3 clinical trials and acts to enhance fear extinction learning in mice and humans. To understand the mechanisms related to MDMA therapeutic effects we conducted experiments to compare monoamine modulation and behavioral responses. We demonstrate a dose-dependent fear extinction enhancing effects of MDMA. Using GPCR-based fluorescent sensors, we demonstrated that MDMA releases 5-HT in the medial prefrontal cortex (mPFC) yet exhibit minimal 5-HT2A-associated behavioral effects. While the 5-HT2A agonist psilocybin had a large head twitch response, different doses of MDMA showed a control equivalent response. Characterizing NE release, we observed that MDMA increases the release of NE in mPFC, which is associated with 5-HT2A-associated behavior suppression. We utilized pharmacological approaches to manipulate the NE pathway. The results indicate interaction between NE release and receptor activation regarding 5-HT2A-associated behavior. Further studies using GPCR-based dopamine sensors will characterize its release and relation to behavioral responses. In addition, 2-photon imaging in vivo will relate monoamine release and pharmacological agonism to structural plasticity. Moreover, monoamine manipulations and prophylaxis MDMA during fear learning and fear extinction can elucidate interactions among neuromodulators in the therapeutic effect of MDMA. These findings suggest interactions between neuromodulators in MDMA's behavioral responses. In conclusion, unveiling MDMA mechanisms of action is imperative to understand its therapeutic effects on PTSD.

Disclosures: A. Rosado: None. **A. Yu:** None. **J. Yang:** None. **J. Rondeau:** None. **A. Basu:** None. **C.J. Pittenger:** None. **Y. Li:** None. **J. Feng:** None. **A.P. Kaye:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Program #/Poster #: PSTR101.10/LL6

Topic: G.07. Post-Traumatic Stress Disorder

Support: US Army Medical Research and Development Command / Military Operations Medical Research Program, project #: MO230047.

Title: Evaluation of Behavioral, Physiological, and Gut Microbiome Responses to Acute Traumatic Psychological Stress: A Rat Model Study

Authors: *J. C. DEMAR, Jr.[1], M. R. RUSLING[1], R. M. DENNETT[1], A. V. HOKE[1], N. I. CRESPO ROSALES[1], S. R. BUTLER[1], A. NADERI[2], A. J. HAN[2], K. T. SHARPES[2], L. P. SIMMONS[2], E. M. SCOTT[2], R. M. TAYLOR[2], E. G. LOWERY-GIONTA[2], A. GAUTAM[1], R. HAMMAMIEH[1];
[1]Med. Readiness Systems Biol. Br., [2]Behavioral Biol. Br. / Performance Assessment and Chem. Evaluation Lab., Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: BACKGROUND: Soldier exposure to psychological traumatic stress during combat can induce acute stress reactions, characterized by extreme anxiety and dissociation. The gut's microbiome modulates brain physiology via intestinal release of psychoactive biomolecules that may mediate the stress response. The aim of the present study was to investigate the interactive effects of gut-microbiome activity and traumatic stress exposure, and to determine the extent to which these effects are sex-dependent. **METHODS:** Male and female rats (n = 6 / group) were exposed to an acute series of traumatic stressors, i.e., predators, foot shocks, and immersion under water. Controls were gently handled. Animals were evaluated at 24 hours post-exposure for behavior on the elevated plus maze, open field, and acoustic startle tests. Fecal samples were obtained, and bacterial microbiomes were assessed by 16s rRNA sequencing. Additional tissues were collected and processed. **RESULTS:** At 24 hours post-stress, behavioral testing revealed significant deficits in both male and female rats, with a more marked stress response in males. Heart histopathology revealed moderate cardiomyocyte cell disturbances in both males and females. In males, there was also a significant stressor-induced increase in alpha-diversity of bacteria taxa, and both sexes had major shifts in beta-diversity of the gut microbiome. Although there were sex-dependent microbiomic profile differences, both sexes exhibited stressor-induced imbalances in the ratio of beneficial to pathogenic species. Bacterial pathways for processing crucial metabolites (e.g., nucleotide degradation) were also negatively affected.
CONCLUSIONS: Our findings indicate that a single day of exposure to traumatic stressors can, within 24 hours, impact performance and health-effects that may be due to, or mediated by, gut-microbiome disruptions. Sex-specific changes were found to strongly correlate with stress susceptibility. The present findings suggest targets of opportunity for discovery and development of novel biomarkers to aid in diagnosis and treatment of acute stress reactions and disorders.
DISCLAIMER: Research was conducted under an institutionally approved animal care and use protocol in compliance with the Animal Welfare Act, and all other Federal requirements. Opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the US Department of the Army or the Department of Defense.

Disclosures: J.C. DeMar: None. **M.R. Rusling:** None. **R.M. Dennett:** None. **A.V. Hoke:** None. **N.I. Crespo Rosales:** None. **S.R. Butler:** None. **A. Naderi:** None. **A.J. Han:** None. **K.T.**

Sharpes: None. **L.P. Simmons:** None. **E.M. Scott:** None. **R.M. Taylor:** None. **E.G. Lowery-Gionta:** None. **A. Gautam:** None. **R. Hammamieh:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.11/LL7

Topic: G.07. Post-Traumatic Stress Disorder

Support: USMRDC MOMRP MO220133

Title: Sex differences in trauma-related behavioral effects using a military-relevant complex traumatic stress model in rats

Authors: *E. M. SCOTT[1,2], A. NADERI[2], C. ALMARODE[2], I. KOBAYASHI[2], J. DEMAR[2], A. HAN[2], K. SHARPES[2], L. SIMMONS[2], R. TAYLOR[2], E. LOWERY-GIONTA[2];
[1]Behavioral Biol., [2]Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Sex differences are commonly identified in chronic trauma-related disorders (e.g., PTSD). However, little is known about sex differences in acute stress reactions and 'combat and operational stress' reactions. There are currently no FDA-approved pharmacologic treatments for either. Determining whether, and the extent to which, there are sex-related differences in stress reactions will potentially streamline development of effective interventions by narrowing the focus of such efforts to sex-related targets of opportunity. To evaluate underlying sex differences, this study implemented the Military Relevant Complex Traumatic Stress (MRCTS) model in rodents. Behavioral outcomes were measured with the elevated plus maze (EPM), open field (OF) test, and acoustic startle response (SR). Data from our previously published and unpublished studies in which MRCTS-exposed Sprague-Dawley rats (82 male, 43 female) were utilized. All rats were exposed to conditions (MRCTS or control) and/or treatment (vehicle solution or no injection). Our first aim was to determine and quantify sex differences on the behavioral measures following stressor exposure. Structural Equation Modeling was used to calculate the interactive effects of sex, anxiety, avoidance, and arousal on behavior. The second aim was to examine sex differences within and between these behaviors, and to characterize sex-related differences in behavior using clustering procedures. A two-way ANOVA with main effects of sex and exposure type and interaction revealed a significant main effect of exposure type with a reduced total distance traveled by MRCTS rats (EPM: $F(1, 121)=37.0$, $p<0.001$; OF: $F(1,121)=4.9$, $p<0.05$) on the elevated plus maze. There was also a main effect of sex, with males exhibiting greater values for stress-like behavior than females (EPM distance: $F(1,121)=54.8$, $p<0.001$; OF distance: $F(1,121)=57.9$, $p<0.001$; SR average startle: $F(1,121)=4.9$, $p<0.05$). It was concluded that (a) the MRCTS model effectively produces stress-like behaviors and (b) males respond more robustly to these stressors. The present findings highlight the importance of accounting for sex differences in stress research. Future efforts to develop

interventions for stress-induced disorders might be facilitated by accounting for sex-dependent differences in response to stressors.

Disclosures: **E.M. Scott:** None. **A. Naderi:** None. **C. Almarode:** None. **I. Kobayashi:** None. **J. DeMar:** None. **A. Han:** None. **K. Sharpes:** None. **L. Simmons:** None. **R. Taylor:** None. **E. Lowery-Gionta:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

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Program #/Poster #: PSTR101.12/LL8

Topic: G.07. Post-Traumatic Stress Disorder

Support: USMRDC MOMRP MO220132

Title: Does pre-traumatic stress inhibition of the anterior cingulate cortex prevent post-stress reactions in rats?

Authors: I. KOBAYASHI, J. C. DEMAR, Jr., ***A. NADERI**, E. M. SCOTT, A. HAN, K. SHARPES, F. ROSSETTI, C. ALMARODE, L. P. SIMMONS, J. LONG, R. M. TAYLOR, E. G. LOWERY-GIONTA;
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Military service members and civilians who are exposed to traumatic stressors (e.g., combat, accidents, assault), often experience acute stress reactions (ASRs). Symptoms of ASRs, such as panic, anxiety, freezing, and dissociation, may begin during the traumatic event and continue for days, significantly undermining an individuals' ability to function in the situation. Currently, no pharmacological interventions for ASRs are available. Prior studies have shown that the dorsal anterior cingulate cortex (dACC) mediates stress and anxiety-related behaviors, and that dACC inhibition results reduces these behaviors. In the present study, chemogenetics were used to determine whether inhibition of dACC activity prior to and during traumatic stressor exposure prevents or reduces stress-induced behavioral performance deficits. Rats (50-day old, n=32) were randomly assigned to one of 4 groups [Stress-Clozapine N-oxide (CNO); Stress-Vehicle; Control-CNO; or Control-Vehicle]. All rats received bilateral intracranial injections of an adeno-associated virus carrying hSyn-driven hM4D(Gi) receptor genes to drive expression of Gi-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the dACC region. Three weeks later, rats were systemically injected with either CNO (1 mg/kg) or vehicle (saline) 45 - 30 minutes prior to the stress or control procedures. Rats in the stress groups underwent our validated Military Relevant Complex Traumatic Stress model procedure, which involves serial exposure to multiple stressors: predator exposure, inescapable footshocks, and underwater submersion. Control rats remained in their home cages. At the 2-hour and 1-day post-stress timepoints, all animals underwent elevated plus maze (EPM), open field (OF), and acoustic startle response (SR) testing. Repeated measures ANOVA and linear

regression analysis were performed, and revealed that stressor exposure resulted in reduced total distance traveled in the EPM ($F = 21.3$, $p < .001$) and OF ($F = 13.3$, $p < .001$) regardless of CNO/Vehicle status. However, dACC inhibition did reduce stress-induced inhibition of exploratory behaviors in the center of the OF ($F = 5.2$, $p = .03$). At the 2-hour timepoint, stressor exposure reduced SR in the vehicle groups ($F = 46.9$, $p < .001$) - an effect that was partially blocked by inhibition of the dACC ($F = 3.4$, $p = .06$). These results indicate that inhibition of the dACC prior to and during the trauma exposure prevents some aspects of post-stress performance deficits, suggesting that processes within the dACC may prove to be targets of opportunity for development of prophylactic interventions for the prevention of ASRs.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Program #/Poster #: PSTR101.13/LL9

Topic: G.07. Post-Traumatic Stress Disorder

Support: T32GM144896
GM082406
8G12MD007579-279
MH116345

Title: Investigating protein candidates associated with susceptibility to stress-induced extinction impairment in Female rodents: a proteomic analysis

Authors: *N. IRIZARRY-MÉNDEZ[1], Y. RIVERA-ESCOBALES[4], M. D. COLON[2], A. HERNÁNDEZ[5], J. T. PORTER[3];
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Abstract: Post-traumatic stress disorder (PTSD) is a condition that develops after experiencing a traumatic event in susceptible individuals. Despite considerable investigation, the precise mechanisms underlying why only certain individuals develop PTSD remain elusive. While research has shown that women are more susceptible to developing PTSD than men, there is still a lack of understanding of the neurobiological mechanisms contributing to this disparity. This is primarily due to the limited number of studies specifically focused on females in clinical and preclinical studies. To address this gap in knowledge, this study aims to examine molecular changes underlying susceptibility to developing impaired fear extinction in female rodents

exposed to single prolonged stress (SPS), a well-studied animal model of PTSD. We hypothesized that changes in the infralimbic cortex (IL) proteome after a traumatic event modulate susceptibility to developing impaired extinction. To test this, adult female rats were subjected to SPS, which consist of two-hour restraint stress, 20 min of forced swim test, and ether exposure until general anesthesia. One week after the SPS, the animals underwent auditory fear conditioning and extinction training. Results showed that similar to people exposed to traumatic events, only a subpopulation of female rats exposed to SPS show impaired fear extinction. This suggests that SPS is a suitable model for studying PTSD-like susceptibility in female rats. To identify protein candidates associated with susceptibility to PTSD-like behaviors, we compared the IL proteome profiles of female rats with poor extinction to those with good extinction. The results revealed that the females with poor extinction exhibited proteomic changes in the IL cortex, suggesting that traumatic stress alters the expression of these proteins to impact IL function and lead to impaired fear extinction. A similar analysis in SPS-exposed male rats found that impaired extinction was associated with distinct IL proteome changes. As a future direction, we will validate proteomic findings by comparing IL protein expression via western blot in a new cohort of SPS-exposed female rats with poor or good extinction. This approach will enable the identification of potential candidate proteins involved in modulating susceptibility to developing impaired fear extinction after exposure to traumatic stress in female rodents which might also translate to susceptibility to develop PTSD in women.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

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Program #/Poster #: PSTR101.14/LL10

Topic: G.07. Post-Traumatic Stress Disorder

Support: Seth Norrholm Faculty Startup Funds

Title: Single prolonged stress effects on conditioned fear extinction retention and fear renewal in Sprague Dawley rats; a fear-potentiated startle (FPS) study.

Authors: *G. W. LEVASSEUR, T. CILLEY, Jr., S. A. PERRINE, S. D. NORRHOLM; Psychiatry & Behavioral Neurosciences, Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: RATIONALE: Posttraumatic stress disorder (PTSD) is known to have a lifetime prevalence of ~8% in US adults, that results in significant functional burden to patients and poses financial burden to the US healthcare system. There is a need for reliable pre-clinical models to understand the underlying neurobiology of PTSD. Single prolonged stress (SPS) is a widely used, 3-pronged stress exposure model that results in the development of PTSD-like characteristics in rats such as abnormal fear learning and increased negative feedback of

corticosterone release, common in those with PTSD. Although the SPS model has been used extensively in translational studies, the extent to which its effects span fear learning models and apply to varying subject characteristics has not been fully explored. For example, the vast majority (>90%) of studies using SPS have excluded females, and have almost always measured freezing as a fear outcome measure. This is despite observations that females are up to 3 times as likely to develop clinical PTSD and rodent freezing may not fully capture the female fear response.
In this study, we use fear potentiated startle to measure fear response post-SPS in both male and female rats. Fear potentiated startle is a more translational measure of fear learning that makes use of the acoustic startle reflex, present in all mammals, to study conditioned fear. Additionally, we expanded conditioned fear testing in the SPS rats to include a test of fear renewal in a novel context. METHODS: 33 Sprague Dawley rats were used in this study (female SPS n=12, male SPS n=9, male control n=12). Rats were conditioned to light (conditioned stimuli, CS) paired with footshock (0.6 mA, unconditioned stimuli) for 30 conditioning trials. Rats underwent 120 extinction trials with unreinforced presentations of the CS. Rats then underwent tests of extinction retention and fear renewal on separate days. RESULTS: All 3 groups show significant levels of fear expression ($p<0.001$) that does not differ between groups. All groups show significant within-session extinction ($p<0.05$). During a test of extinction retention, SPS rats show an extinction retention deficit that is not present in the control (male $p=0.006$, female $p=0.0005$). During a test of fear renewal, male SPS rats show a significant return of fear ($p=0.0116$) that is not present in female SPS rats ($p=0.088$). FUTURE STUDIES: In upcoming studies we plan to causally investigate the contribution of norepinephrine in the amygdala to the SPS extinction retention deficit with inhibitory DREADDs.

Disclosures: G.W. LeVasseur: None. **T. Cilley:** None. **S.A. Perrine:** None. **S.D. Norrholm:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH R01 MH073136
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T32 MH119049-02
T32 DA050558-03
UROP

Title: Spatial and emotional memories are impacted by acute, multiple concurrent stresses in an estrogen dependent manner

Authors: *R. E. HOKENSON[1], S. A. SAMRARI[2], G. D. ANGELES[3], Y. CHEN[3], Y. H. ALAM[4], A. K. SHORT[3], M. T. BIRNIE[3], J. C. LAUTERBORN[2], C. JANG[4], C. M. GALL[2], T. Z. BARAM[3];
[1]Anat. & Neurobio., Univ. of California, Irvine, Irvine, CA; [2]Anat. & Neurobio., [3]Pediatrics, [4]Biol. Chem., Univ. of California Irvine, Irvine, CA

Abstract: Background: Posttraumatic stress disorder (PTSD) is a debilitating neuropsychiatric disorder characterized by both intrusive memories and deficits in declarative memory. PTSD has long been known to follow chronic stress and trauma. However, acute *traumatic* events such as mass shootings, assault, or natural disasters - events composed of simultaneous physical, social, and emotional components - are increasingly recognized as significant contributors to PTSD. We have established that multiple acute concurrent stresses (MAS) enduringly impair hippocampus dependent memory and destroy dorsal CA1 synapses in males. In females, those stressed during early-proestrus (high estrogens) were likewise impaired while females stressed during estrus (low estrogens) were surprisingly protected from MAS. Notably, hippocampal estrogen levels are reportedly higher in males and proestrous females, both vulnerable to MAS, than in resilient estrous females. These findings suggest that high levels of hippocampal estrogens may enable MAS-induced cognitive disruptions and raise the possibility that they might also contribute to the emergence of PTSD-like behaviors. **Methods:** We tested the role of hippocampal estrogens in both spatial memory deficits following immediately after MAS and in the emergence of PTSD like behaviors over weeks by blocking estrogen receptor activation. We probed estrogen receptor (ER) contribution by treating mice with selective ER blockers and examined the impact of MAS in transgenic mice with selective, conditional deletion of ERα or ERβ from hippocampus (under the CamKII promoter). Impacts on cognition were assessed through hippocampus-dependent memory tests. To investigate PTSD-like consequences of MAS, or augmented susceptibility to a second stressor, we examined behaviors in response to MAS-associated cues or in response to a second, acute stress. **Results:** MAS enduringly disrupt spatial and emotional memory in males, and in and females stressed during proestrus. Blocking estrogen receptors prevented memory deficits after MAS in males and in proestrous females. We identified ERβ in females and ERα in males as those receptors mediating the deleterious effects of estrogen. We found that MAS augments the response to additional stressors and MAS-associated cues weeks after the original trauma (MAS). Ongoing experiments are probing the role of estrogen in the emergence of PTSD-like behaviors.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.16/LL12

Topic: G.07. Post-Traumatic Stress Disorder

Support: National Center for PTSD
Duraviva
Connecticut Mental Health Center
Yale University Interdepartmental Neuroscience Graduate Program,
NINDS NS041228

Title: The effects of a single dose of ketamine on mGluR7 in a mouse model of PTSD

Authors: *J. M. COUDRIET, Y. PARK, M. WU, S. MOHAMMED, M. J. GIRGENTI, A. CHE;
Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Posttraumatic stress disorder (PTSD) is a debilitating mental disorder occurring in the aftermath of significant trauma exposure. While more frequently utilized for treatment-resistant major depressive disorder (MDD), ketamine has gained increasing clinical interest as a potential treatment for PTSD symptoms. However, its pharmacological mechanisms of action have not been fully elucidated. Metabotropic glutamate receptors have been shown to play a key role in mediating the rapid antidepressant effects of ketamine due to their modulatory effects on glutamate transmission. In this study, we examined the effects of ketamine on metabotropic glutamatergic receptor 7 (mGluR7) in a mouse model of single prolonged stress (SPS). Adult male mice that underwent SPS exhibited elevated anxiety- and depression-related behaviors accompanied by altered inhibitory but not excitatory synaptic transmission in the medial prefrontal cortex (mPFC) 7-14 days post-stress. A single intraperitoneal injection of ketamine (10 mg/kg) or the mGluR7 agonist AMN082 (10 mg/kg) 24 hours post-stress improved behavioral outcomes and restored inhibitory synaptic transmission in SPS-exposed mice. Moreover, both ketamine and AMN082 administration led to a long-lasting sequestering of mGluR7 to the nucleus and a reduction of cytosolic mRNA levels, as well as diminished mGluR7-mediated synaptic depression at the inhibitory synapse. We hypothesize that the glutamate surge after ketamine administration leads to prolonged mGluR7 internalization and decreased binding, contributing to its anxiolytic efficacy. Further understanding of the pharmacological mechanisms of action for ketamine could lead to novel targets for the treatment of PTSD and MDD.

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Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.17/LL13

Topic: G.07. Post-Traumatic Stress Disorder

Title: MDMA in the treatment of anxiety and PTSD: a behavioral assessment in rodents

Authors: *K. WALKER[1], E. ESNEAULT[2], C. FROGER-COLLEAUX[1], E. CAMPEROS[1], A. LECOQ[1], A. HERNIER[1];
[1]Porsolt S.A.S., Le-Genest-Saint-Isle, France; [2]Porsolt S.A.S., Le Genest St Isle, France

Abstract: 3,4-methylenedioxymethamphetamine (MDMA) is a psychoactive compound categorized as a psychedelic and classified as illegal due to its ability to be abused for recreational use. Nevertheless, over decades, MDMA-assisted psychotherapy has demonstrated effectiveness in reducing Post-Traumatic Stress Disorder (PTSD) symptoms, renewing interest in its potential use for the treatment of anxiety and associated disorders.
The present study aimed to evaluate the acute effects of MDMA in the marble burying test, a screening test of anxiolytic-like activity in rodents. It was also assessed for locomotor activity. Acute and sub chronic effects of MDMA were also evaluated in a PTSD-like model in mice and rats using a Fear Extinction protocol. Rodents associate conditioned stimulus (CS) as a tone with electrical shocks previously received (unconditioned stimulus, US). Repeated exposure to the cue in the absence of electrical shocks leads to a progressive suppression of the fearful reaction evoked by the cue through an extinction process, which represents a key process in exposure-based therapies for PTSD at the clinical level.
In the marble burying assay, MDMA administered acutely dose-dependently decreased the number of marbles buried over a 30-minute exposure period in the dose-range 2.5 - 10 mg/kg i.p., while an increased locomotor activity was observed from 2.5-3 mg/kg.
The Fear Extinction protocol showed that MDMA administered acutely at 5.6 mg/kg i.p. prior to the first extinction session significantly decreased the percentage of freezing time as compared to vehicle-treated mice ($p<0.001$). This effect was still observed 24 hours later during a drug-free extinction session ($p<0.01$). Similar effects were observed at 5 mg/kg i.p. in the rat during the first extinction session but when MDMA was repeatedly administered prior the following 3 extinction sessions, the percent of freezing was progressively increased, suggesting a potential tolerance to MDMA.
Taken together, these results showed an anxiolytic-like effect of acute MDMA treatment in the mouse as indicated by the decreased of the number of marbles buried and the percent of freezing. On another hand, increased locomotor activity was reported, even at the low dose tested in the mouse and fear extinction was impaired after sub-chronic treatment in rats, suggesting psychostimulant effects of MDMA and its dual pharmacological property on PSTD depending on treatment conditions and/or species.
The results confirm the potential of psychedelics in the treatment of anxiety-related disorders and the need to test new therapies in different relevant pre-clinical models.

Disclosures: K. Walker: A. Employment/Salary (full or part-time):; Porsolt S.A.S. **E. Esneault:** A. Employment/Salary (full or part-time):; Porsolt S.A.S. **C. Froger-Colleaux:** A. Employment/Salary (full or part-time):; Porsolt S.A.S. **E. Camperos:** A. Employment/Salary (full or part-time):; Porsolt S.A.S. **A. Lecoq:** A. Employment/Salary (full or part-time):; Porsolt S.A.S. **A. Hernier:** A. Employment/Salary (full or part-time):; Porsolt S.A.S..

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.18/LL14

Topic: G.07. Post-Traumatic Stress Disorder

Title: Mdma promotes fear extinction learning in mice

Authors: *R. WU, Z. WANG, J. SU, G. HUANG, Y. ZHENG, Z. ZHANG, Z. LI, J. CAO, Y. XIN, D. XU;
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Abstract: Post-traumatic stress disorder (PTSD) is a chronic and devastating disorder. 3,4-methylenedioxymethamphetamine (MDMA), a synthetic analog of amphetamine, has been shown to significantly improve the symptoms of PTSD patients in combination with psychotherapy. However, the mechanisms underlying the efficacy of MDMA in the treatment of PTSD remain elusive. While extinction learning plays a key role in clinical exposure-based psychotherapy for PTSD, less evidence suggested a role of MDMA in the extinction process. Here, by adopting the translational animal models of PTSD (fear conditioning and single prolonged stress), we aimed to study the bio-behavioral underpinnings of MDMA in the process of extinction learning. Firstly, in the fear conditioning assay, mice were conditioned with a cued fear procedure and then underwent extinction trainings. MDMA was administered prior to the extinction. We found that MDMA decreased freezing to the tone during extinction trainings. Furthermore, mice that received MDMA also showed decreased freezing in the extinction test compared with the vehicle group, suggesting that the effect of MDMA may be persistent. Secondly, by using fiber photometry, we tested the activity of neurons in the Infralimbic (IL) cortex in the extinction of the single prolonged stress (SPS) model. We found that a single prolonged stress resulted in deficits in extinction learning as compared with the sham group. Most importantly, the mice from SPS group also showed significant reduction in IL activity in the fear extinction test. As IL is implicated in regulating fear extinction, it might be the key region for the effects of MDMA in the treatment of PTSD, which merits further studies.

Disclosures: R. Wu: None. **Z. Wang:** None. **J. Su:** None. **G. Huang:** None. **Y. Zheng:** None. **Z. Zhang:** None. **Z. Li:** None. **J. Cao:** None. **Y. Xin:** None. **D. Xu:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.19/LL15

Topic: G.07. Post-Traumatic Stress Disorder

Support: R00 DA047426-01A1
PI Startup Funds

Title: Cell-type specific calcium transient recordings in rat NAcore during stress and stress conditioned responses

Authors: *M. L. ALLEN, F. CHAURE, M. E. MEYERINK, J. TABORDA, C. GARCIA-KELLER;
Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Acute stress can precipitate the onset of different neuropsychiatric disorders such as post-traumatic stress disorder (PTSD) which is hallmarked by symptoms of reexperiencing/intrusions, hyperarousal, and avoidance. Studies have indicated the prevalence of comorbidity of PTSD and substance use disorder is about 30-50%. GABAergic medium spiny neurons (MSN) in the nucleus accumbens core, structure in involved in reward and motivation, are vulnerable to morphological changes due stress and addiction. These neurons express D1- or D2- dopaminergic receptors and are known to code for different responses where, generally, D1-MSN activation promotes drug-seeking, and D2-MSN activation inhibits drug-seeking. Here, we want to understand if these responses relate to active and passive coping mechanisms that we see in response to stress conditioned stimulus (stress CS), and if these responses can predict resilience and susceptibility phenotypes that may be triggered by stress.
D1- or D2- cre rats were virally injected with a cre-dependent GCaMP virus and a GRIN lens was implanted. After 4 weeks, animals were sham or restrained for two hours in a container with an odor, that becomes the stress CS. Twenty-one days after stress, animals were placed in an open field box with bedding at one end and the stress CS, at the other end to complete a defensive burying (DB) task. This task was done for 3 consecutive days to also evaluate extinction to stress CS (days 21, 22 and 23 after stress). Active copying mechanism is characterized by increased burying while passive is characterized by increased immobilization/freezing response. We performed within subject longitudinal analysis of calcium dynamics in D1- and D2-MSN in freely moving animals while performing a task using a miniature microscope.
We have seen a trend towards an increase D2-MSN average event rate and cumulative events during the restraint session. Moreover, studying accumbal cell-specific Ca^{2+} transients during repetitive exposure to stress CS we showed: 1) increased Ca^{2+} dynamics in D1-MSN encode passive behavior when the animal is exposed for the first time to the stress CS in a DBT (DB1) and 2) cognitive flexibility to extinguish to stress CS is subjacent to plasticity in D1-MSN (DB1 vs DB3). We also follow the activity of 60% of cells in rat NAcore over 3 consecutive DB sessions.
Insights into how stress and stress cues, and their relationship with drug-related activity $Ca2+$ dynamics can provide a foundation for understanding circuit-level stress and addiction pathogenesis. We believe that in the future this can allow us to study susceptible vs resilient populations.

Disclosures: M.L. Allen: None. **F. Chaure:** None. **M.E. Meyerink:** None. **J. Taborda:** None. **C. Garcia-Keller:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

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Program #/Poster #: PSTR101.20/LL16

Topic: G.07. Post-Traumatic Stress Disorder

Support: K99DA047426-01A1
PI's start-up funds

Title: Stress Cues Exposure Induced Excitatory Plasticity in NAcore Pentapartite Synapse

Authors: M. MEYERINK, J. TABORDA, M. ALLEN, ***C. GARCIA-KELLER**;
Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Epidemiological studies indicate that acute life-threatening events increase the incidence of post-traumatic stress disorder(PTSD), and a diagnosis for PTSD carries 30-50% comorbidity with substance use disorder (SUD). Presentation of drug-associated cues evoke synaptic potentiation in the tetrapartite synapse, which includes the pre- and postsynaptic neurons,astrocytes, and extracellular matrix (ECM) in the nucleus accumbens core (NAcore). Given the overlap between theenduring adaptations produced by stress and drug use, we hypothesized that animals exposed to a stress-conditionedstimulus (stress CS) elicit synaptic potentiation in NAcore and differential coping responses in a defensive burying task(DBT). We found that animals exposed to stress-CS showed an increase in active and passive coping responses, and theywere associated with synaptic potentiation in NAcore quantified as: increased spine density and spine head diameter,increased metalloproteinase-9 activity (enzyme that catalyzes proteins from the ECM) and astrocyte retraction fromsynapses compared to control animals. Since extensive chronic stress literature showed the relevance of microglia in spineremodeling and in depression models, we proposed to study microglia as the fifth component of the pentapartite synapse,and the possible trigger of the NAcore neuroadaptations in our stress model. We studied microglia morphology after thestress CS or neutral odor (NS) exposure during DBT using confocal microscopy and three different analysis software (3DMorph, IMARIS and Image J). We observed constitutive and transient changes in cell territory (maximum space occupied),cell volume (maximum number of pixels), ramification index, number of endpoints, number of IBA-1+ cells, and shollanalysis in female as well as male stressed animals exposed to NS or CS in comparison to sham NS animals. Overall, datashowed increased amoeboid microglia morphology that suggests increased phagocytic functions. Despite that, one of themost well-known phagocytic microglia functions is synaptic pruning, after acute stress, we have consistently shownincreased number of spines in medium spiny neurons of NAcore. Future experiments are design to understand what is therole of microglia phagocytic functions in the pentapartite synapse during stress CS exposure, and for example determineif in adulthood microglia or astrocytes (which also have been shown their role in trimming spines) are pruning the spinesin baseline conditions and if that function is changed after acute stress.

Disclosures: **M. Meyerink:** None. **J. Taborda:** None. **M. Allen:** None. **C. Garcia-Keller:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.21/LL17

Topic: G.07. Post-Traumatic Stress Disorder

Support: R00 DA047426-01A1
PI's Start-Up Funds

Title: Optimization of 3DMorph Software for Microglia Morphology Analysis of 30-min Acute Stress Rat Model

Authors: *J. P. TABORDA, M. E. MEYERINK, F. CHAURE, M. ALLEN, C. GARCIA-KELLER;
Pharmacol. and Toxicology Dept., Med. Col. of Wisconsin, Wauwatosa, WI

Abstract: The main focus of our laboratory is to study the long-term neuroadaptations induced by acute stress that underlie vulnerability to drug use. We showed that exposure to an acute stressor enhances drug intake, and triggers a number of enduring adaptations within corticostriatal synapses of the nucleus accumbens core (NAcore, a structure associated with reward and motivation), which resemble drug-induced adaptations. Literature from chronic stress disorder have shown the crucial role of microglia in spine morphology architecture and neuro-inflammation conditions. Our stress model (2-hours restraint) showed that after the stressful event there is a robust increase in spine density and spine head diameter in NAcore, and blood pro-inflammatory cytokines. Therefore, we ought to understand the role of microglia during the stress session and its long-term consequences. The activity of microglia is closely related to its morphology, having a dichotomy in which amoeboid microglia have phagocytic functions and ramified microglia have surveying functions. We decided to evaluate the role of microglia within 30min of the stress session. After stress we perfused the animals, collected the brain, sliced it at 100 um and used Iba-1 antibody to label microglia. We took z-stacked pictures with a confocal microscope (Leica SP8). We analyzed the pictures by using an optimized and updated version of the 3Dmorph software (York et al, 2018). This software reconstructs microglial pictures and measures the Cell Territory, Cell Volume, Ramification Index parameters, and few more, which are useful to analyze their morphology and therefore interpret their activity. We analyzed a male and female cohort of Long Evans rats (n=12 stress and n=12 sham), we had statistical difference in different parameters, but specifically, with ramification index we saw an increase of amoeboid microglia suggesting an increase in phagocytic functions on stressed male rats compared to the sham males that showed more ramified microglia. Additionally, we had no statistical difference between sham and stress females in the ramification index, which indicates sex differences in the stress group. However, at baseline sham females showed increased number of IBA-1 positive

cell that was reduced in the stressed group. This data suggests that the plasticity after stress in NAcore may be induced or triggered by the microglial neuro-inflammation state generated during the stress. However, more experiments need to be performed to evaluate our hypothesis and understand the mechanism. The lab plans to further optimize 3DMorph and publish updates on our GitHub: https://github.com/CGK-Laboratory

Disclosures: J.P. Taborda: None. **M.E. Meyerink:** None. **F. Chaure:** None. **M. Allen:** None. **C. Garcia-Keller:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.22/LL18

Topic: F.03. Stress and the Brain

Title: Single Prolonged Stress Alters Inflammatory Markers in Male Rats

Authors: *C. V. CHEN[1], S. PLAS[2], T. H. LAUTEN[1], E. REED[1], A. J. CASE[1], I. LIBERZON[3]; [1]Texas A&M Univ., Bryan, TX; [2]Texas A&M Univ., College Station, TX; [3]Psychiatry, Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Post-traumatic stress disorder (PTSD) is a chronic, debilitating disorder that can emerge following exposure to a traumatic event. It is the 4th most common psychiatric disorder, with lifetime prevalence in the US at 6.8%. PTSD patients show increased levels of pro-inflammatory markers, known to be precursors to other health conditions, which PTSD patients are at increased risk for. To assess whether our PTSD model affects inflammation, we exposed rats to SPS trauma and assessed spleen and plasma inflammatory markers. Our data indicate that IL-1β, IL-17A, IL-22 and TNF-α increased in spleen, and IL-1β, IL-6, IL-4, IL-5 and IFN-α increased in plasma of animals exposed to SPS compared to control counterparts. In addition, variability in inflammatory measures, especially in the SPS group, can shed light on individual differences related to risk and resiliency. Here, we replicate the same pro-inflammatory markers seen in PTSD patients using the SPS animal model of PTSD, indicating that SPS can be used as a valid model for the study of inflammation in PTSD and other disease comorbidities.

Disclosures: C.V. Chen: None. **S. Plas:** None. **T.H. Lauten:** None. **E. Reed:** None. **A.J. Case:** None. **I. Liberzon:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.23/LL19

Topic: F.03. Stress and the Brain

Title: Unexpected Factors Affect Replicability and Experimental Outcome

Authors: C. CHEN[1], S. PLAS[1], H. CARDENAS[1], ***M. PEREZ**[2], I. LIBERZON[1];
[1]Texas A&M Univ. Hlth. Sci. Ctr., College Station, TX; [2]Texas A&M Univ. Syst. Hlth. Sci. Ctr., Laredo, TX

Abstract: Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that affects 3.5 percent of adults every year, and is the fourth most prevalent mood disorder. Our laboratory utilizes an internationally known rodent model of PTSD, single prolonged stress (SPS), to determine changes in the brain associated with this condition. Since we recently relocated from the University of Michigan to Texas A&M University, it was imperative to first replicate our expected SPS-induced phenotype before conducting any new research and confidently interpreting data. After several rounds of experiments and modifications, we replicated the expected SPS-induced extinction recall deficits. Noteworthy, several parameters unrelated to experimental design were identified to contribute to experimental outcome. It is worth considering external factors during experimental data interpretation to rule out type II error.

Disclosures: C. Chen: None. **S. Plas:** None. **H. Cardenas:** None. **M. Perez:** None. **I. Liberzon:** None.

Poster

PSTR101. Preclinical Models of Post-Traumatic Stress Disorder

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR101.24/LL20

Topic: F.03. Stress and the Brain

Title: Heart function as measured via echocardiogram is not altered by different estrous stages in female rats

Authors: C. CHEN, Z. CHEN, W. LUO, ***T. PATEL**, R. KHAN, I. LIBERZON;
Texas A&M Univ. Syst. Hlth. Sci. Ctr., Bryan, TX

Abstract: Heart disease is the number one cause of death and disability in women. Interestingly, women with posttraumatic stress disorder (PTSD) have almost four times the risk for developing heart disease after the initial mental disorder diagnosis. In order to study this phenomenon and be able to interpret data accurately, we sought to determine whether heart function as measured via echocardiogram would vary in intact adult female rats. Our data indicate that estrous cycle stage does not modulate measures of heart function obtained via echocardiogram.

Disclosures: C. Chen: None. **Z. Chen:** None. **W. Luo:** None. **T. Patel:** None. **R. Khan:** None. **I. Liberzon:** None.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.01/LL21

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

Support: NIH Grant AA030505

Title: A cost effectiveness analysis of deep brain stimulation compared to medical management for the treatment of alcohol use Disorder and alcoholic liver disease.

Authors: *O. A. ABIOLA[1], N. E. MILLER[1], H. JALAL[2], K. MOUSSAWI[1];
[1]Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [2]Sch. of Epidemiology and Publ. Hlth., Univ. of Ottawa Sch. of Med., Ottawa, ON, Canada

Abstract: Alcohol is the most misused drug globally and is associated with high mortality risk due to alcohol-related complications like liver cirrhosis and hepatocellular carcinoma. The current treatments for alcohol use disorder (AUD) have limited efficacy, and new treatments are needed to reduce relapse rates. Deep brain stimulation (DBS) could be an effective treatment option for severe AUD and its complications. However, before this treatment can be implemented into standard care, its cost effectiveness has to be determined. We developed a one-way sensitivity analysis to determine the probability of success necessary for DBS to impart the same costs and effectiveness (measured in quality adjusted life years (QALY)) in patients with AUD with or without alcoholic liver disease (ALD). We then created a Monte Carlo Simulation to determine the possible choice outcomes given the uncertainty of our model inputs by producing a random sample of 1000 iterations. All data entered into our models were adapted from previous studies. The results of our one-way sensitivity analysis showed that independent of the probability of DBS success, DBS does not equate the expected costs of medical management; however, for AUD patients with ALD, DBS is cost saving at a 44% probability of success. This analysis also showed that DBS imparts an equal amount of QALYs as medical management at a 27% success rate for AUD patients and at 24% for AUD patients with ALD. Our Monte Carlo simulation showed that DBS is not cost effective for the general AUD population a year after the intervention given the $100,000 per QALY willingness to pay threshold. However, for AUD patients with ALD, it is 83% more cost effective than medical management at the same threshold. Overall, should it prove efficacious, DBS may be cost-effective for some subpopulations of patients with AUD.

Disclosures: O.A. Abiola: None. **N.E. Miller:** None. **H. Jalal:** None. **K. Moussawi:** None.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.02/LL22

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA, IRP

Title: Focal Transcranial Magnetic Stimulation (TMS) of rat mPFC reduces the motivation for cocaine intake

Authors: *S. HOFFMAN, C. LI, H. NGUYEN, Y. DUAN, Z. MA, Y. YANG, H. LU;
NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD

Abstract: Transcranial magnetic stimulation (TMS) shows promise in reducing cocaine craving in patients with cocaine use disorder. Our lab developed a new TMS paradigm, high-density theta burst stimulation (hdTBS), which shows more promising aftereffects than conventional intermittent theta burst stimulation. In rats, activity in the medial prefrontal cortex (mPFC) is compromised with prolonged cocaine use. The goal of this study was to assess the potential effects of hdTBS on rats' motivation for cocaine intake using a progressive ratio (PR) schedule. Male Sprague Dawley rats (n=8) were surgically implanted with an intravenous (IV) catheter, allowing for cocaine IV self-administration. Rats were trained to self-administer cocaine (0.5 mg/kg/infusion) for 3 weeks on a fixed ratio 1 (FR1) schedule. TMS pulses were delivered using a hdTBS stimulator and a rodent specific focal TMS coil developed in-house. A headpost was implanted on the rat skull, which served as the reference point to effectively guide the focal point of the TMS coil to the mPFC. After surgery, rats were retrained on the FR1 schedule for 3 days. We used the PR breakpoint to measure the rats' motivation to take cocaine. There were 3 stages of PR testing: baseline (3-4 days), treatment (3 days), and post-treatment (2 days). During the treatment phase, rats received either 6-pulse hdTBS (n=4) or sham stimulation (n=4), and during baseline and post-treatment phases, all rats received sham stimulation. Our results showed that hdTBS decreased the rats' motivation to take cocaine during hdTBS treatment ($p < 0.05$, paired t-test), and for 2 days post-hdTBS treatment ($p < 0.05$, paired t-test), but motivation for cocaine did not change in rats receiving sham stimulation. There was also a decreasing trend of the rats' breakpoints from day 1 to 3 of hdTBS treatment. Overall, hdTBS to the rat mPFC effectively reduced the rats' motivation to take cocaine.

Disclosures: S. Hoffman: None. **C. Li:** None. **H. Nguyen:** None. **Y. Duan:** None. **Z. Ma:** None. **Y. Yang:** None. **H. Lu:** None.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.03/LL23

Topic: G.09. Drugs of Abuse and Addiction

Support: NAD Research, Inc.

Title: Evaluating and refining assessment of withdrawal symptoms associated with opioid and alcohol use disorders using intravenous administration of nicotinamide adenine dinucleotide detox protocols

Authors: *S. L. BROOM[1,2], T. OLDS[3,2], R. F. MESTAYER[2];
[1]Psychology, William Carey Univ., Hattiesburg, MS; [2]NAD Research, Inc., Springfield, LA;
[3]Springfield Wellness Ctr., Springfield, LA

Abstract: Introduction: Hospitalizations, overdoses and deaths due to substance use disorders (SUD) are increasing demand for healthcare involving detox and support for long term recovery. Treatment facilities using medical assistance therapy show success, however they rely on use of opioid agonists to achieve stabilization. Nicotinamide Adenine Dinucleotide (NAD) is a coenzyme of vitamin B3, and patented in the 1960's as a treatment for alcohol and drug abuse. A clinic in Springfield, LA developed intravenous (IV) NAD administration protocols for treatment of withdrawal (WD) symptoms associated with SUD; retrospective analyses showed a significant decrease in drug cravings while maintaining sobriety over time. Recent protocols incorporated standardized assessments with clinic derived questionnaires to provide comprehensive measures of efficacy. This pilot study examined withdrawal symptoms associated with opioid (OUD) and alcohol use disorder (AUD) following IV NAD administration in a group of 26 patients (pts). Methods: Pts received treatment at Springfield Wellness Center comprised of IV infusions of NAD (500-1500mg) with supportive WD medications and oral vitamins for up to10 days ranging from 5-10 hours daily. Clinicians measured WD symptoms using the Clinical Opioid Withdrawal Scale (COWS), Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar), and symptom checklist (0-10 scale) recorded in nurses' notes. Descriptive analyses were performed on composite scores, individual symptoms and comparison with previous pt data. Positive drug screens and interrupted treatment days were noted. Findings: Majority in both groups were male, with AUD pts averaging 10 years older. Both groups completed at least 4 days (1 pt) up to the expected 10 days (17 pts). Twelve/Fourteen OUD pts and 2/12 AUD pts had positive drug screens on their first treatment day (prior to IV). One pt (OUD) received 100mg subcutaneous NAD injections plus 800mg iontophoretic patch in place of IV. COWS scores averaged in the mild range, with anxiety, pulse rate, and GI upset most noted. CIWA-Ar scores averaged in the mild range, with hand tremor and anxiety most noted. Composite scores for both groups were consistent with previous pt data across first 5 treatment days, however, cravings were lower and more variable from D1-D10. Discussion: Results show that NAD is an effective supportive detox treatment for AUD and OUD. Furthermore, data suggest that self report ratings with COWS/CIWA-Ar improves measures of WD. Future studies should include training in administration/scoring of assessment forms and encourage patient participation during initial and follow-up phases.

Disclosures: S.L. Broom: F. Consulting Fees (e.g., advisory boards); NAD Research, Inc. **T. Olds:** A. Employment/Salary (full or part-time):; Full time employee at Springfield Wellness Center. Other; Serves on Science Advisory Board for NAD Research, Inc. **R.F. Mestayer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Molecular World Health. Other; Serves on Science Advisory Board for NAD Research, Inc..

Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.04/LL24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 1R01AA029674

Title: Effects of novelβ-lactam, MC-100093, in ethanol intake and GLT-1 expression in brain of alcohol-preferring rats

Authors: *A. ALOTAIBI[1], S. TRAVAGLIANTI[1], W. WONG[1], M. ABOU-GHARBIA[2], W. CHILDERS[2], Y. SARI[1];
[1]Pharmacol. and Exptl. Therapeut., Univ. of Toledo, Toledo, OH; [2]Dept. of Pharmaceut. Sci., Temple Univ. Sch. of Pharm., Philadelphia, PA

Abstract: Alcohol use disorder (AUD) results in prolong alteration of several neurotransmitters. Extensive studies showed that alcohol consumption affects glutamate homeostasis in several brain regions, including the prefrontal cortex (PFC) and nucleus accumbens (NAc). Glutamate transmission is regulated in majority by glutamate transporter 1 (GLT-1). Studies from our lab showed that ceftriaxone, a beta-lactamase antibiotic, reduced ethanol drinking and normalized extracellular glutamate concentrations in NAc, and this effect was associated with upregulation of GLT-1. Recently, our lab identified a novel β-lactam, MC-100093, which was shown to normalize GLT-1 expression in NAc. Considering this discovery, the current study aimed to investigate the impact of MC-100093 on ethanol consumption and GLT-1 expression in medial PFC subregions such as prelimbic PFC (PL) and infralimbic PFC (IL). Male P rats (n=16) were divided in three groups: a) Control water group was exposed to water only for 5 weeks and received i.p. saline on Week 6 for 5 days; b) Saline group was exposed to free choice of ethanol (15% and 30% and water) for 5 weeks, and received saline (i.p.) on Week 6 for 5 days; and c) MC-100093 group was exposed to free choice of ethanol for 5 weeks and received MC-100093 (100 mg/kg/day, i.p.) for 5 days on Week 6. The results showed that MC-100093 attenuated ethanol intake and decreased ethanol preference. Furthermore, MC-100093 increased GLT-1 expression in both subregions of medial PFC such as PL and IL. These findings suggest that MC-100093 may have potential therapeutic benefits in treating AUD.

Disclosures: A. Alotaibi: None. **S. Travaglianti:** None. **W. Wong:** None. **M. Abou-Gharbia:** None. **W. Childers:** None. **Y. Sari:** None.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Program #/Poster #: PSTR102.05/LL25

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH, NIDA, Z1A-DA000611
NIH, NIDA, Z1A-DA000389

Title: Exploring the neurochemical actions of atypical dopamine transporter inhibitors: probing sex and strain differences in mouse accumbens dopamine dynamics using FSCV

Authors: *G. TANDA, M. K. BARTOLE, A. CHEN, C. S. JONES, A. H. NEWMAN, M. HERSEY;
NIH, NIDA IRP, Baltimore, MD

Abstract: Understanding the neurochemistry underlying psychostimulant use disorder (PSUD), an increasingly prevalent health condition with no FDA-approved pharmacological treatments, is essential for developing efficacious therapeutics. Potential therapeutic options currently being explored for the treatment of PSUD include atypical dopamine transporter (DAT) inhibitors that produce neurochemical and behavioral effects inconsistent with those elicited by typical, cocaine-like, psychostimulants, which interactions with DAT are largely thought to account for their misuse and dependence. The atypical DAT inhibitor, modafinil, an agent approved for the treatment of sleep disorders, is a low-affinity DAT inhibitor that has been suggested as a potential PSUD medication, but its efficacy appears limited to selected addicted populations. In order to provide a PSUD pharmacotherapy with efficacy in a broader population, novel analogs of modafinil like JJC8-088 and JJC8-091, have undergone preclinical testing as potential PSUD medications. In this work, we employ fast scan cyclic voltammetry (FSCV) to probe dopamine (DA) dynamics in the nucleus accumbens shell (NAS) of C57BL/6 and Swiss Webster male and female mice after administration of typical (cocaine, WIN 35,428, and JJC8-088) and atypical (*R*-modafinil and JJC8-091) DAT inhibitors. We found that cocaine (3 and 10 mg/kg; i.p.) slowed DA clearance in both male and female mice but produced more robust increases in evoked NAS DA in female mice. WIN 35,428 (0.1 mg/kg; i.p.) produced a robust increase in NAS DA as well as slowed DA clearance in both male and female mice. *R*-modafinil (10 and 32 mg/kg; i.p.) produced dose-dependent increases in evoked NAS DA and slowed DA clearance in male and female mice. JJC8-088 (10 and 32 mg/kg; i.p.) produced increases in evoked NAS DA in female and male mice. Finally, JJC8-091 (10 and 32 mg/kg; i.p.) produced limited increases in evoked NAS DA but did slow DA clearance in male and female mice. We find that some differences in sensitivity to DAT inhibitors by the strain of mouse did emerge. For instance, administration of JJC8-088 produced more robust increases in maximum evoked NAS DA in Swiss Webster than in C57BL/6 mice, a phenomenon that is worth exploring further. In conclusion, we have begun to tease out how sex and strain differences may alter the neurochemical effects of DAT targeting and highlight how this may help focus research progressing toward effective treatment options for PSUD.
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Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.06/LL26

Topic: G.09. Drugs of Abuse and Addiction

Support: RISE NIH 5R25GM060665-22
CUNY Grant 80209-0426

Title: Assessing drug permeability and concentration of (-)-stepholidine derivatives following voluntary oral administration to determine its effectiveness in treating methamphetamine use disorder.

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Abstract: Effective pharmacological agents to treat methamphetamine (MA) use disorder (MUD) have not been developed. The chronic use of MA rapidly increases dopamine (DA) levels, resulting in drug-reward/reinforcement behaviors in the striatum. Targeting the dopaminergic system is a potential, underexplored mechanism for MUD therapeutic intervention. SPD is a tetrahydroprotoberberine alkaloid, that displays a D1 agonist /D2 antagonist /D3 antagonist profile and with anti-addiction and memory enhancing properties. Despite, the pharmacodynamic profile of SPD as a promising potential MUD therapeutic agent, it displays poor oral bioavailability, limiting its therapeutic utility. The purpose of this study is to investigate the properties of SPD derivatives as potential, orally delivered prodrugs with improved SPD brain exposure. We hypothesize that modifications to the phenolic groups of SPD via prodrug moieties will enhance its pharmacokinetic properties, improving oral bioavailability and delivery of SPD into the brain, following voluntary oral administration (VOA). A mouse model of VOA was used to deliver the drugs - SPD, and the potential prodrugs tetrahydropalmatine (THP) and stepholidine diacetate (SPDD). Liquid chromatography-tandem mass spectrometry (UPLC- MS/MS) was used to evaluate the permeability and concentration of the drugs in C57Bl/6J male mice brain. A single dose of SPD (10 mg/kg) was administered, and brains assessed at 5-, 10-, 15-, and 30-min post VOA. For THP, a single 20 mg/kg dose was administered, and brains assessed at 15-, 30-, 60-, and 120-min post VOA. SPD was not detected at any time point in brain after VOA. Upon administration of THP, we successfully detected THP at all time points in brain, but there was no detection of SPD. However, following a single oral dose of SPDD (10 mg/kg), we detected stepholidine 5-,10-,15-, and 30-min post VOA in

brain. These results indicate that SPDD improved the oral bioavailability and brain exposure of SPD and similar investigations of other potential SPD prodrugs are warranted. The results also suggest that orally administered THP is not effective for SPD brain delivery. We must further evaluate SPDD as an anti-METH addiction agent using a previously validated model of voluntary oral methamphetamine administration (VOMA). This will include characterizing any underlying change in DA receptor expression in the striatum.

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Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

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Program #/Poster #: PSTR102.07/LL27

Topic: G.09. Drugs of Abuse and Addiction

Title: Differential effects of enantiomers of the novel benzofuran derivative 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (bk-5-mapb) in rats trained to discriminate stimulants and psychedelics.

Authors: *R. L. BURROUGHS[1], M. J. BAGGOTT[2], L. E. BAKER[1];
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Abstract: MDMA is a mixed stimulant-psychedelic/entactogen under clinical investigation for medication-assisted psychotherapy. Although MDMA is used recreationally and presents some risk for abuse, phase III clinical trial outcomes indicate it will likely be FDA-approved for PTSD treatment. Adverse side effects, such as anxiety and cardiovascular toxicity may limit its clinical use. Investigations of novel molecules with structural similarities to MDMA are underway to develop potential pharmacotherapies with comparable clinical benefits and reduced side effects. Preclinical drug discrimination assays offer exceptional utility to classify novel psychoactive substances. This study employed three drug discrimination experiments to characterize the interoceptive stimulus effects of the two enantiomers of 1-(1-benzofuran-5-yl)-2-(methylamino)propan-1-one (BK-5-MAPB), a benzofuran with structural and pharmacological similarities to MDMA. In the first experiment, nine adult male rats were trained to discriminate the stimulant, d-amphetamine (0.5 mg/kg). In experiment two, eight adult male rats were trained to discriminate the hallucinogen, DOM (0.5 mg/kg) from saline. In the third experiment, eight male rats were trained to discriminate d-amphetamine (1.0 mg/kg) and MDMA (1.5 mg/kg) from saline in a three-lever drug discrimination procedure. Stimulus substitution tests were conducted in all three experiments with (S)-BK-5-MAPB, (R)-BK-5-MAPB, and a non-racemic mixture (65% S/35% R) of BK-5-MAPB (0.32-2.54 mg/kg, IP). In the AMPH-trained rats in experiment one, both (S)- and (R)-BK-5-MAPB produced dose-dependent increases in AMPH-lever responding and full substitution at the highest dose, whereas, (S)-BK-5-MAPB produced only

partial substitution and (R)-BK-5-MAPB did not substitute for DOM in experiment two. The non-racemic mixture produced partial substitution in AMPH-trained, but not DOM-trained rats. The enantiomers also produced disparate effects in rats trained to discriminate AMPH from MDMA in experiment three; (S)-BK5-MAPB fully substituted for MDMA in 5 of 6 rats tested, whereas (R)-BK-5-MAPB fully substituted for AMPH in 4 of 6 rats tested and the nonracemic mixture fully substituted for MDMA in 3 of 6 rats tested. These findings indicate (S)-BK-5-MAPB has similar interoceptive stimulus effects to both MDMA and AMPH, whereas (R)-BK-5-MAPB has primarily stimulant effects. (S)-BK-5-MAPB, either as a pure enantiomer or as a non-racemic mixture, may have promise as an MDMA-like therapeutic. Further research is required to assess the pharmacology of BK-5-MAPB, especially cardiovascular effects and potential neurotoxicity.

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Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Time-dependent effect of exercise on addictive-like behavior induced by toluene

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Abstract: Exercise has an important impact to attenuate addictive behavior; however less is known about the duration of the exercise to have those positive effects. In this study we evaluate the development of addictive-like response induced by toluene, a compound widely found in inhalants used with intoxication purposes, and then we analyze the effect of different times of exercise to attenuate the expression of addictive-like response induced by this compound. For this purpose Swiss-webster male mice (10-12 per group) which were exposed to toluene (4000 ppm/30 min per day/5 days a week for 4 weeks) were used. Control animals (air) were not administered with this inhalant. Addictive-like response was evaluated with the behavioral sensitization model, in which locomotor activity of mice was recorded the first day and then each week of exposure to toluene or air. In the second part of the experiment animals were housed in cages with running wheels during different times a day, i.e. 1, 2, 4 or 24 h/day for 4 weeks. At the end of the experiments all mice were challenged with a dose of toluene 4000 ppm and their locomotor activity was registered. Results show individual differences in the display of behavioral sensitization, some animals were sensitized and some others were not. Exercise from 2 to 24 h/day seems to attenuate expression of behavioral sensitization; however the individual analysis showed that in animals with a history of toluene exposure, and a treatment with 4 and 24 h/day of exercise produces a most homogeneous reduction in the locomotor sensitization. Altogether, this data shows that as in humans, individual differences are found in animals exposed to drugs of abuse, including inhalants. Exercise efficacy depends on the regimen of administration, which may explain the controversial results in some experiments conducted with exercise. Exercise deserves future study as a potential treatment for addictive behavior in inhalant users in rehabilitation.

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Poster

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Program #/Poster #: PSTR102.09/MM1

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01 AA028680

Title: Differential Effects of Environmental and Social Enrichment on Alcohol Drinking in Mice

Authors: *M. C. JOHNSON, J. A. ZWEIG, Y. ZHANG, A. E. RYABININ;
Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: It is well understood that social isolation results in adverse health consequences and contributes to the development of various neuropsychiatric disorders including, depression, anxiety, and substance use disorders. Indeed, as a consequence of the recent COVID-19 pandemic and increased social distancing, hazardous alcohol drinking has risen. In rodent models, social isolation in un-enriched housing conditions, such as a standard shoebox cage,

enhances alcohol drinking behavior through the lack of stimulation and absence of conspecific social reward. Previous work has attempted to model isolation-enhanced alcohol drinking behavior by either group housing animals to provide social enrichment, or by making their housing conditions more complex to provide environmental enrichment (EE). Interestingly, our lab has recently shown that C57BL/6J mice who are both environmentally and socially enriched consume significantly more alcohol than their EE but isolated counterparts in a two-bottle choice drinking paradigm (2BC). From this, we suspected that the relationship between EE, social enrichment, and alcohol drinking is more complex than previously thought. Thus, we investigated the relationship between environmental and social enrichment on alcohol drinking in male and female C57BL/6J mice by varying both the housing conditions and the environment's social complexity within a 2BC paradigm. Adult mice underwent 2BC while housed in either standard shoebox cages or larger and more environmentally complex "Herdsman-2" cages (HM2) in either isolation or housed in groups of four for one week. Daily alcohol and water consumption was recorded and calculated by dividing intake by bodyweight of each animal (g/kg) for all groups. A mixed design repeated measures ANOVA of detected in a significant main effect of both housing condition, social condition, and an interaction effect of housing and social conditions. Indeed, alcohol drinking is elevated in isolated and non-EE mice compared to group-housed mice in the same conditions. Meanwhile, alcohol drinking is lower in isolated but EE mice than it is in group-housed EE mice. The effects were alcohol-specific and not accompanied by similar effects on water intake. These results demonstrate that housing enrichment and social enrichment both influence alcohol drinking behaviors, however, their specific effects on alcohol drinking are dependent on one another.
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Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.10/MM2

Topic: G.09. Drugs of Abuse and Addiction

Title: A Novel Class of Psychedelic Ibogaine Analogs Demonstrate Efficacy in Preclinical Models of Opioid Use Disorder Without Cardiotoxicity

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Gilgamesh Pharmaceuticals, New York, NY

Abstract: Rationale: Opioid use disorder results in significant mortality and distress worldwide. Although several pharmacotherapies exist, these are of limited effectiveness and there is a dire need for novel therapeutic approaches. Ibogaine, a psychoactive alkaloid, shows potential in interrupting opioid use and maintaining long-term abstinence, but is associated with well-

documented, serious cardiac safety risks. Here we describe a new class of synthetic iboga alkaloids, "oxa-iboga", which are kappa opioid receptor (KOR) agonists that retain the therapeutic efficacy of ibogaine without its cardiotoxicity.
Objective: To investigate the potential efficacy and safety of the representative oxa-iboga compound GM-3009 as a novel therapeutic for opioid use disorder. The presented studies aimed to elucidate GM-3009's effects on opioid intake and opioid withdrawal, as well as its cardiac safety profile.
Methods: The efficacy of GM-3009 was tested compared to the active ibogaine metabolite noribogaine in rodent models of opioid use disorder, including self-administration and withdrawal. Its impact on cardiotoxicity was evaluated in human cardiomyocytes, also compared to noribogaine. Lastly, the analgesic effect of GM-3009 was evaluated using the tail-flick and hot plate assays as a pharmacodynamic measure of KOR target engagement and its effect on locomotion in the open field was evaluated as a measure of sedative-like side effects. All results were interpreted in the context of pharmacokinetic exposure. Results: In rodents, GM-3009 and its more active enantiomer dose-dependently suppressed oxycodone self-administration and attenuated behavioral signs of opioid withdrawal with a greater potency than noribogaine. Further, GM-3009 lacked the pro-arrhythmic effects of noribogaine in human cardiomyocytes, even at concentrations well above therapeutically efficacious exposure levels. In the tail-flickanalgesia assays, GM-3009 showed potent and dose-dependent antinociceptive effects in an efficacious dose range similar to that observed in self-administration, while in the open field, GM-3009 exhibited reduced sedative-like effects compared to a prototypical KOR agonist.
Conclusion: Oxa-iboga compounds, and specifically GM-3009, may serve as promising novel pharmacotherapies for opioid use disorder. They offer an improved cardiac safety profile compared to ibogaine and noribogaine, while matching or improving upon these reference compounds in preclinical models of opioid use disorder. Further research is warranted to establish the safety and efficacy of GM-3009 or other oxa-iboga compounds in humans.

Disclosures: **M. Cunningham:** A. Employment/Salary (full or part-time):; Gilgamesh Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gilgamesh Pharmaceuticals. **A. Kruegel:** A. Employment/Salary (full or part-time):; Gilgamesh Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gilgamesh Pharmaceuticals. **D. Sames:** A. Employment/Salary (full or part-time):; Columbia University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gilgamesh Pharmaceuticals.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR102.11/MM3

Topic: G.09. Drugs of Abuse and Addiction

Support: ZIA-AA000242

Title: Pcsk9 inhibition attenuates alcohol-associated neuronal oxidative stress and neuroinflammation.

Authors: *J. WAGNER[1], L. PARK[2], P. MUKHOPADHYAY[3], A. HAMANDI[5], P. PACHER[4], F. W. LOHOFF[6];
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Abstract: Alcohol use disorder (AUD) is a chronic condition which is associated with neuroinflammation, neuronal oxidative stress, and ultimately neurodegenerative processes. Recently, PCSK9 inhibition has been proposed as a novel therapeutic approach for reducing alcohol-associated liver inflammation; however, the effects of PCSK9 inhibition on brain are largely unexplored. In this study, we evaluate the effects of alirocumab, a monoclonal antibody that reduces systemic LDL-C via PCSK9i, on CNS pathology in a rat model of chronic alcohol exposure. Alirocumab (50 mg/kg) or vehicle was administered weekly for 6 weeks in animals receiving a 35% ethanol liquid diet. Alcohol exposure upregulated PCSK9 in brain while alirocumab treatment significantly attenuated PCSK9 levels, upregulated neuronal LDLR, and reduced oxidative stress in neurons and in brain vasculature (NT, oxLDL, p22phox). PCSK9i lowered alcohol-induced recruitment of microglia in cortex and hippocampus (Iba1), reduced the expression of pro-inflammatory markers (CCL2, CXCL3 and TNF) in whole brain tissue and attenuated the upregulation of adhesion molecules in brain vasculature (ICAM1, VCAM1, e-selectin). Our data provide new evidence that PCSK9i decreases oxidative stress and neuroinflammation in the brain after chronic alcohol exposure. Future studies are needed to elucidate in detail how PCSK9 signaling affects the brain under chronic alcohol exposure.

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Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Topic: G.09. Drugs of Abuse and Addiction

Support: PhRMA Foundation Faculty Starter Grant in Drug Discovery

Title: Novel psychoplastogen influence opioid-induced neurobehavioral plasticity.

Authors: K. LOOSCHEN[1], M. MAULIK[2], K. CORRIVEAU[2], H. ARIAS[3], ***S. MITRA**[2];
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Abstract: Opioid use disorder is a major public health crisis in the US and worldwide. The current pharmacotherapeutic strategies fail to provide long-term symptom alleviation. Psychoplastogens belong to a new class of therapeutic compounds possessing robust abilities to produce a rapid measurable change in neuronal function and structure that can be long-lasting. Despite being examined as a potential therapeutic option in depression and post-traumatic stress disorder, the anti-addictive properties of psychoplastogens remain elusive. Here we examine the pharmacological effect of a novel psychoplastogen, DM506, on heroin-related behaviors. Our data reveal that DM506 reduces heroin-induced behavioral plasticity in a sex-dependent manner that is concomitant with distinct neuroplasticity in the medial prefrontal cortex.

Disclosures: K. Looschen: None. **M. Maulik:** None. **K. Corriveau:** None. **H. Arias:** None. **S. Mitra:** None.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Program #/Poster #: PSTR102.13/MM5

Topic: G.09. Drugs of Abuse and Addiction

Title: Behavioral and neurochemical characterization of 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (BK-5-MAPB) enantiomers

Authors: *C. B. JOHNSON[1], R. BURROUGHS[2], M. BAGGOTT[4], D. WALTHER[5], M. BAUMANN[6], L. BAKER[3];
[1]Psychology, WMU, Kalamazoo, MI; [3]Psychology, [2]Western Michigan Univ., Kalamazoo, MI; [4]Tactogen, Redwood City, CA; [5]Designer Drug Res. Unit, IRP, NIDA, NIH, DHHS, Baltimore, MD; [6]IRP, NIDA, NIH, Baltimore, MD

Abstract: The entactogen, 3,4- methylenedioxymethamphetamine (MDMA) is currently being evaluated in phase 3 of clinical trials as an experimental adjunct to psychotherapy for those that have post-traumatic stress disorder. MDMA is also a popular abused substance with cardiovascular risks and metabolic side effects that may limit its clinical use. Characterization of the behavioral and neurochemical effects of novel psychoactive substances (NPS) can aid in the development of safer alternative therapeutic agents. This study characterized the locomotor stimulant and discriminative stimulus effects of 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (BK-5-MAPB) enantiomers and differentiated their pharmacokinetics and neurochemical actions.16 male Sprague-Dawley (SD) rats trained in a two-lever operant drug discrimination procedure to discriminate 1.5 mg/kg MDMA from saline. Stimulus substitution tests were conducted with S- and R-BK-5-MAPB (0.32, 0.64, 1.27 mg/kg IP). Locomotor activity was assessed in three separate cohorts of male SD rats (N=6) following a single injection of saline or each enantiomer; doses (0, 0.32, 0.64, 1.27 mg/kg IP) were assessed once per week in ascending order. In a separate set of experiments, monoamine release and uptake inhibition at SERT, DAT, and NET were assayed using rat synaptosomes and [^{3}H]5-HT or [^{3}H]MPP+ as

substrate. In separate cohorts of male SD rats (N=4), plasma concentrations were assayed after 1.27 and 3.81 mg/kg IP and pharmacokinetics were estimated. S-BK-5-MAPB produced dose-dependent increases in MDMA-lever responses and full substitution at 0.64 and 1.27 mg/kg; R-BK-5-MAPB produced less than 30% MDMA-lever responding. Both enantiomers increased distance traveled in a dose-dependent manner that was statistically significant compared to saline-treated controls. Both enantiomers were substrate-type releasers at all three transporters. The S-enantiomer displayed an MDMA-like profile with greater potency at SERT than DAT (DAT/SERT ratio of 0.6), while R-BK-5-MAPB had a typical stimulant profile (DAT/SERT ratio of 18). Both enantiomers had higher potency at DAT than NET (DAT/NET ratios of 2.7 and 1.9 for the S- and R- enantiomer, respectively). Pharmacokinetics differed between the enantiomers, with R-BK-5-MAPB showing a lower Cmax and higher clearance than its counterpart.
S- and R- BK-5-MAPB produce behavioral and neurochemical actions similar to MDMA and stimulants, likely through monoamine transporters. Because they have reduced potency at NET, these novel substances may have utility in elucidating the contributions of NET to MDMA-like and typical stimulant effects.

Disclosures: **C.B. Johnson:** A. Employment/Salary (full or part-time):; WMU. 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.; Tactogen. **R. Burroughs:** A. Employment/Salary (full or part-time):; WMU. 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.; Tactogen. **M. Baggott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactogen. **D. Walther:** A. Employment/Salary (full or part-time):; NIDA. **M. Baumann:** A. Employment/Salary (full or part-time):; NIDA. **L. Baker:** 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.; Tactogen.

Poster

PSTR102. Addiction: Drug Discovery and Treatment

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R21DA055558

Title: Benchmarking a larval zebrafish phenotypic assay to identify agents which reverse the effects of synthetic opioids

Authors: *A. S. WISNER[1,2], J. DURIC[3], C. N. GORRELL[4], W. S. MESSER, Jr.[3], F. S. HALL[3], F. E. WILLIAMS[3], I. T. SCHIEFER[5];
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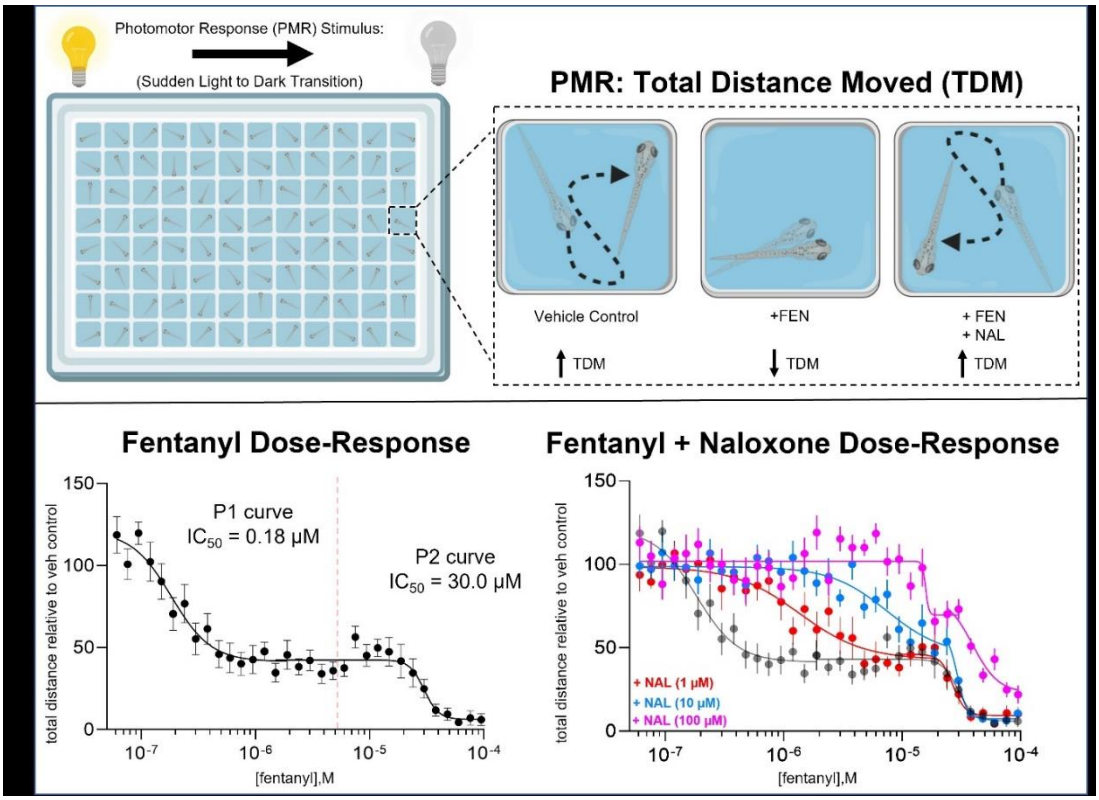
Abstract: Introduction: Most cases of death resulting from opioid overdose are associated with synthetic opioids, particularly fentanyl. Unfortunately, the first-line treatment for opioid overdose, naloxone (Narcan®), exhibits decreased effectiveness in cases of synthetic opioid overdose. In this study, we demonstrate the potential of a larval zebrafish photomotor response (PMR) behavioral assay to identify novel agents which reverse the effects of fentanyl overdose. Methods/Results: To characterize the effects of fentanyl on 7-dpf (days post fertilization) zebrafish larvae; we generated a rigorous 33-point (n=8 for each point [performed in duplicate]) dose-response curve for fentanyl (1nM - 100µM) in a 20-min PMR assay (10-min light / 10-min dark). Data analysis demonstrated the most significant effects on the total distance traveled (relative to vehicle) in the 2-min period following photic stimulus. We observed two distinct inhibitory phases that were classified as follows: phase 1 (P1) represented by a ≤50% reduction of locomotion (IC50 = 0.18µM); and phase 2 (P2) with a ≥50% reduction of locomotion (IC50 = 30.0µM). The 33-point dose response was then repeated in the presence of 1, 10 or 100µM naloxone. Naloxone was able to shift the fentanyl IC50 for phase 1 (1µM naloxone = 7.5-fold shift [IC50 = 1.35µM]; 10µM naloxone = 50-fold shift [IC50 = 8.85µM]; 100µM naloxone = 87-fold shift [IC50 = 15.8µM]), but had little to no effect on the fentanyl IC50 for phase 2 (1µM naloxone = negligible change [IC50 = 27.8 µM]; 10µM naloxone = negligible change [IC50 = 29.5µM]; 100µM naloxone = a 25% shift [IC50 = 39.2µM]). Conclusion: Naloxone blocks the sedative effects (P1) of fentanyl but fails to reverse the effects associated with overdose (P2), except at 100µM. Future Directions: Screening of compound libraries will be carried out in a similar fashion to identify novel chemical classes that show equivalent, or improved activity compared to naloxone.



Disclosures: **A.S. Wisner:** None. **J. Duric:** None. **C.N. Gorrell:** None. **W.S. Messer:** Other; Dr. Messer holds patents for the use of muscarinic agonists in the treatment of neurological disorders and is the founder and president of Psyneurgy Pharmaceuticals LLC.. **F.S. Hall:** None. **F.E. Williams:** None. **I.T. Schiefer:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.01/MM7

Topic: G.09. Drugs of Abuse and Addiction

Support: The Foundation of Hope (SF)
R01 AA028782 (CWH)
P60 AA011605 (CWH)

Title: Transmembrane ampa regulatory protein gamma-8 (TARP γ-8) is required for the induction and expression of behavioral sensitization to cocaine and morphine in mice

Authors: *S. FACCIDOMO[1], C. WHINDLETON[2], R. WELCH[3], R. K. JENKINS[4], J. L. HOFFMAN[4], J. LEE[4], C. W. HODGE[5];
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Abstract: *Background:* The elevated locomotor response following repeated administration of a drug over time, known as behavioral sensitization, is a common model to examine the underlying neuronal plasticity associated with repeated drug use. Repeated administration of both cocaine and morphine upregulates AMPAR GluA1 subunit expression in the nucleus accumbens (NAC), which alters the strength of these synapses, leading to enduring changes in brain plasticity. Transmembrane AMPA regulatory proteins (TARPs) bind to the GluA1 subunit to regulate receptor trafficking and the subtype TARP γ-8, is highly expressed in NAC-projecting brain regions, such as the prefrontal cortex (PFC) and amygdala (AMY), both of which modulate glutamatergic tone converging on the NAC. Both genetic and pharmacological inhibition of TARP γ-8 reduces alcohol self-administration in mice, suggesting that it could be an effective target to modulate the rewarding properties of other drugs of abuse. *Objective:* To test whether TARP γ-8 is required for full induction and expression of cocaine and morphine sensitization and to assess TARP γ-8 dependent gene expression changes associated with behavior. *Methods:* Separate groups of adult, C57BL/6J TARP γ-8 wildtype (WT; +/+) and knockout mice (KO; -/-) were repeatedly injected with 10 mg/kg cocaine, 10 mg/kg morphine or saline to induce behavioral sensitization. On days 1, 4, and 7 locomotor activity was measured for 30-min following drug injection. After 7 days of withdrawal, mice were injected with either cocaine or morphine and tested for the expression of behavioral sensitization. Brain tissue was collected immediately after this final test to assess potential TARP γ-8 dependent changes in TARP-AMPAR (*Cacng8, Cacng2, Gria1, Gria2, CamkII)* and dopamine (*Drd1, Drd2*) gene expression in the PFC, NAC, and AMY. *Results*: In WT mice, repeated injections of cocaine and morphine resulted in a robust induction and expression of behavioral sensitization; for both drugs this locomotor enhancement was absent in KO mice. In accordance with the literature, cocaine-sensitized WT mice showed a significant down regulation of *Drd2* and a significant upregulation of *Gria2* in the PFC. Notably, no significant changes these genes were seen in KO mice. Interestingly, we found a significant drug-induced upregulation of *Cacng8* in the NAC of WT mice only. *Conclusion:* TARP γ-8 is required for full induction and expression of cocaine- and morphine-induced behavioral plasticity and the molecular mechanisms within the PFC to NAC circuit may be critical for TARP γ-8's regulation of behavioral sensitization.

Disclosures: S. Faccidomo: None. **C. Whindleton:** None. **R. Welch:** None. **R.K. Jenkins:** None. **J.L. Hoffman:** None. **J. Lee:** None. **C.W. Hodge:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.02/MM8

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

Support: HRSA-T99HP39202

Title: Changes of locomotor activities in ASIC2a knock-out mice in response to cocaine administration

Authors: R. JILAKARA[1], J. ZAHN[1], O. SAPPINGTON[2], X. ZHA[2], M. WACKER[2], P. MONAGHAN-NICHOLS[2], ***X. CHU**[2];
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Abstract: Acid-sensing ion channels (ASICs) are heavily expressed in the brain, with ASIC1a and ASIC2 being the most prominent. The role of ASICs in cocaine addiction is not fully understood. We and others have shown that ASICs contribute to cocaine addiction by using ASIC1 and ASIC2 knock-out mice. In the present studies, ASIC2a knock-out mice were generated by using CRISPR/Cas9 technology at our university animal core. We investigated the role of ASIC2a in response to acute and chronic cocaine administration in adult (8 to 10 weeks old) ASIC2a knock-out mice. We analyzed behavioral activities by measuring total distance traveled, horizontal activity, and stereotyping time of the individual mouse. Cocaine mice were injected with 20 mg/kg of cocaine, and control mice were injected with 20 mg/kg of saline (intraperitoneal injection). Cocaine was also administered in a chronic fashion by giving mouse 20 mg/kg of cocaine or saline once a day for five days (i.p. injection). After the five days, all mice were given a two-week withdraw period. At the end of the two-week interval, all mice were then given a challenge injection of cocaine at a dosage of 10 mg/kg (i.p. injection), regardless of prior cocaine/saline status. Their behavioral activity was measured at this time as well. Acute injection cocaine triggers increased behavioral activities including total distance, Horizontal activities, and stereotyping time. In the chronic cocaine administration model (20 mg/kg of cocaine once daily for 5 days, i.p. injection), there was a statistically significant increase in activity measurements over baseline. Additionally, there was a statistically significant decrease in activities of the mice who were injected with 20 mg/kg of saline over the 5 days. There was no statistically significant change in activities for either the cocaine or saline group after their challenge injection of 10 mg/kg of cocaine. Our results suggest that ASIC2a plays a critical role in cocaine use but not in cocaine sensitization.

Disclosures: R. Jilakara: None. **J. Zahn:** None. **O. Sappington:** None. **X. Zha:** None. **M. Wacker:** None. **P. Monaghan-Nichols:** None. **X. Chu:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.03/MM9

Topic: G.09. Drugs of Abuse and Addiction

Support: MRC Grant PJAG/464
BBSRC Grant PJAG/450
MRC Grant PJAG/517

Title: Drivers of Amygdala Plasticity in the Development of an Incentive Cocaine Seeking Habit

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Abstract: The use of cocaine and heroin among young Europeans and Americans has been steadily increasing over the past decade. As such it has never been more important to understand the mechanisms whereby some individuals switch from recreational controlled drug use to habitual and eventually compulsive drug seeking and taking, a hallmark feature of Substance Use Disorder. In humans, non-human primates, and rodents a shift occurs in the neural locus of control over behaviour from the ventral to the dorsolateral striatum (DLS) over the course of a history of drug use which sets the stage for the development of compulsivity and the tendency to relapse. We have recently shown that this shift is driven by a functional transition from the basolateral nucleus (BLA), involved in goal-directed behaviour, to the central amygdala (CeN), involved in habits. In rats trained to seek cocaine under the influence of the conditioned reinforcing properties of a cocaine-paired cue, as measured under a second order schedule of reinforcement (SOR), cocaine seeking initially depends on the BLA-NaCc circuit, but when it becomes well-established and habitual, drug seeking relies on dopaminergic mechanisms in the aDLS, the persistence of which depends on the CeN. The mechanisms underlying these intra-amygdala functional transitions have not been elucidated. In order to address this progressive shift from early to established cocaine seeking, male Sprague-Dawley rats were trained to seek cocaine under a SOR for 3 or 21 days, time points at which drug seeking is known to be independent of, or mediated by the CeN - aDLS habit system, respectively. Having demonstrated, using patch-clamp electrophysiological recordings of BLA and CeN neurons that the excitability of the former decreases when cue-controlled cocaine seeking becomes habitual, we used qPCR to investigate the mRNA levels of potassium and sodium channels involved in intrinsic excitability and those of glutamate-dependent synaptic plasticity markers. In addition, we combined the bilateral intra BLA infusion of a retrograde tracer with RNAscope against markers of cellular activity and plasticity to identify upstream ensembles that may drive this decrease in the excitability of the BLA. The results from these experiments show that the switch in neural control over drug seeking when it becomes habitual is accompanied by a decrease in BLA activity which may enable control by the CeN and could be driven by both amygdala-intrinsic plasticity mechanisms and synaptic plasticity stemming from prefrontal projections. These findings could indicate multiple mechanisms by which to break maladaptive drug seeking habits.

Disclosures: S.I. Stiebahl: None. **M. Puaud:** None. **S. Jones:** None. **D.J. Belin:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.04/MM10

Topic: G.09. Drugs of Abuse and Addiction

Title: Cocaine's influence on reinforcement learning in macaques

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Abstract: The neural structures that drive reinforcement learning significantly overlap with the midbrain dopaminergic reward pathway. We have previously described a reinforcement learning network comprised of three functionally and anatomically separate components: (1) volition to respond to stimuli via an orbitofrontal-accumbens circuit, (2) trial and error exploration via a caudate-dorsolateral prefrontal circuit, and (3) habitual performance of learned responses via a putamen-premotor circuit. Previous work by our group demonstrated that electrical stimulation in the head of the caudate, whose medium spiny neurons respond to unexpected trial and error outcomes, accelerates reinforcement learning. Addictive stimulants increase dopaminergic activity in these same circuits. Our overarching hypothesis is that stimulant-induced inflation of dopaminergic release at nodes within the reinforcement learning network results in a highly potent form of learning and pathological cue-response conditioning that persists well into periods of abstinence and thereby increases the risk of relapse upon subsequent exposure to overlearned stimuli. To investigate the influence of addictive stimulants on learning, we evaluated the effects of cocaine on learning rates and cognitive flexibility in macaques performing an associative learning task. We compared the average cue-response learning curves on days with noncontingent cocaine injections (0.5 mg/kg, intramuscular) to those on days with saline injections. Telemetric monitoring of heart rate and respiratory rate revealed no autonomic response to this dose. We made point-to-point comparisons to identify learning trials that were significantly different across treatment groups ($\alpha = 0.2$, two-tailed comparison) and then cluster-based permutation testing to identify significant regions of contiguous performance differences ($1x10^6$ permutations, $\alpha = 0.05$). Cocaine accelerated learning in one macaque with a slower baseline learning rate ($p < 0.02$) but there was no detectable difference in performance in another animal with faster baseline learning. These experiments examined the effect of noncontingent cocaine administration on associative learning. Ongoing work will evaluate cocaine administered as a reward contingent on correct behavioral responses to specific stimuli in the same associative learning task. The impact of contingent cocaine on learning rates, reversibility of cocaine-rewarded responses, and error patterns will be quantified and compared to noncontingent cocaine and saline controls.

Disclosures: C.M. Feigen: None. **N.J. Killian:** None. **R. Falcone:** None. **E.N. Eskandar:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.05/MM11

Topic: G.09. Drugs of Abuse and Addiction

Support: CONAHCYT graduated scholarship N. 479345

Title: Peripheral brain derived neurotrophic factor, depression, and anxiety after 5-Hz rTMS protocol in patients with cocaine/crack dependence

Authors: *E. MORELOS-SANTANA[1], R. ALCALÁ-LOZANO[1], Y. FLORES-MEDINA[1], P. AGUILAR-VELAZQUEZ[1], N. VEGA-RIVERA[2], J. J. GONZÁLEZ-OLVERA[3], E. M. ESTRADA[2];
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Abstract: Brain derived neurotrophic factor (BDNF) has a remodeling role in cocaine/crack use disorder (CUD) and peripheral increases in this factor is associated with recovery periods in depression. Repetitive transcranial magnetic stimulation (rTMS) has shown a craving-reduction effect in CUD, however, potential identifiable biomarkers of rTMS effect as peripheral BDNF and a potential association with mood changes in CUD have not been explored. This study followed a 2-week double blind sham-controlled RCT methodology to explore possible changes in peripheral BDNF, depression and anxiety after a 5Hz-rTMS or placebo intervention. Stimulation protocol was administered for 2 weeks (weekdays) and consisted of 5000 pulses per day (2 sessions of 5 Hz, 50 pulses per train, 10 s. inter-train interval and 30 minutes of inter-session interval at 100 % of motor threshold). The stimulation was applied over dorsolateral prefrontal cortex (lDLPFC) localized by BEAM F3 method. Standardized Hamilton depression and anxiety symptoms inventories were administered. Commercial ELISA kit was used to the measurement of serum BDNF and preliminary percentages of change are presented (n=8). Urine substance consumption status(positive/negative) at T0, each 72 hours until T1 was determined. The study followed the Declaration of Helsinki and was approved by the local ethics committee. Participants gave a written informed consent. Two-way ANOVA was performed to analyze results. Twenty participants completed basal (T0) and post rTMS or sham intervention (T1) (10 participants rTMS and 10 participants sham group. No factor interaction (time*group) was founded in ANOVA. A time effect founded in depression ($F(1,36)=11.56$, p < 0.01, partial eta sq=0.24) and anxiety ($F(1,36)=6.96$, $p=0.01$, partial eta sq=0.16). Preliminary BDNF analysis of 4 sham participants showed an increase of 2, 7.8, 15.5 and 29.1%. Otherwise, one participant in rTMS group showed an increase of 6.1% and the other 3 participants showed a decrease of 1.2, 3.1 and 29.1% in peripheral levels of BDNF. Augmentation in peripheral BDNF levels have been related to depression and anxiety improvements, however, we observed improvements in depression and anxiety in both groups also with peripheral BDNF decreases. Some studies have shown peripheral BDNF increases during inpatient interventions, this could help to understand increases observed in patients in the sham group. These findings show a possible effect of rTMS

on peripheral levels of BDNF and could help to elucidate a different dynamic of this neurotrophin in CUD in comparison to previous studies in depression.

Disclosures: **E. Morelos-Santana:** None. **R. Alcalá-Lozano:** None. **Y. Flores-Medina:** None. **P. Aguilar-Velazquez:** None. **N. Vega-Rivera:** None. **J.J. González-Olvera:** None. **E.M. Estrada:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.06/MM12

Topic: G.09. Drugs of Abuse and Addiction

Support: NRF 2022R1A6A1A03054419

Title: The involvement of TRPA1 in cocaine addiction in prefrontal-accumbens glutamatergic pathway

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Abstract: Although cocaine use disorder (CUD) is still a severe global health problem, there is no approved pharmaceutical treatments yet. Growing evidence indicates that repeated exposure to cocaine leads to changes in glutamate transmission in mesocorticolimibc system. Transient receptor potential ankyrin 1 (TRPA1) channel has emerged recently as potential target to treat psychostimulant dependence. This study aims to elucidate relevance of medial prefrontal cortex (mPFC) to nucleus accumbens (NAc) glutamatergic pathway in cocaine addiction and evaluate modulating effects of TRPA1. To investigate the role of TRPA1 in NAc on cocaine-induced addictive behaviors, several behavioral tests (conditioned place preference (CPP) and CPP reinstatement (RI), hyperlocomotion, and behavioral sensitization) were performed in C57BL/6J mice, while regulating TRPA1 in NAc with TRPA1 antagonist, A967079, treatment. Further, optogenetic and chemogenetic activation of mPFC to NAc pathway were made in the same behavioral tests while regulating TRPA1. Brain tissues were collected from NAc and mPFC regions and underwent western blot and ELISA-based assay for assessing molecular changes. We found that intra-NAc infusions of A967079 inhibited both cocaine CPP acquisition and RI and altered cocaine-induced mice locomotion. Next, we targeted mPFC glutamatergic afferents in NAc using viral expression. When those neurons are specifically activated by optical stimulation, it produced CPP in mice which was attenuated by pretreatment of A967079. Consistently, when mPFC to NAc glutamatergic pathway was activated by chemogenetic stimulation, it produced hyperlocomotion and locomotor sensitization which were attenuated by intra-NAc infusions of A967079. However, intra-NAc infusions of A967079 did not affect the challenge of locomotor sensitization induced by chemogenetic stimulation. Glutamate levels

were increased by cocaine injection both in the mPFC and NAc which was inhibited by A967079 pretreatment. Moreover, the protein levels of NR2B, and pCAMKII/CAMKII were significantly upregulated in cocaine-treated group which was attenuated in A967079-treated group. Current studies suggest that TRPA1 is deeply related to cocaine addictive behaviors. TRPA1 can regulate cocaine addiction presumably by hindering glutamatergic transmission extending from mPFC to NAc and CAMKII signaling might be the underlying mechanism. (supported by a grant 2022R1A6A1A03054419 from the NRF)

Disclosures: **Y. Lee:** None. **Y. Kim:** None. **W. Kook:** None. **S. Hwang:** None. **D. Kim:** None. **S. Lee:** None. **C. Jang:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.07/MM13

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA046373
NIH Grant DA007288

Title: Hdac5 intrinsic enzymatic activity limits cocaine-seeking behavior

Authors: *D. J. WOOD[1], E. TSVETKOV[2], S. COMTE-WALTERS[2], L. BALL[2], E. M. ANDERSON[2], M. TANIGUCHI[2], C. COWAN[2];
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Abstract: Repeated use of illicit drugs produces long-lasting associations between the drug experience and environmental features through stable neuroadaptations in the brain's reward circuitry. Drug-cue associations can serve as potent motivators of drug seeking in abstinent individuals long after drug cessation. In rodents, the epigenetic enzyme histone deacetylase 5 (HDAC5) functions in the nucleus accumbens (NAc) during active drug use to limit future cue-induced drug seeking. HDAC5 shuttles steadily between the cytoplasm and the nucleus, but cocaine and heroin produce a nuclear accumulation of HDAC5 that limits drug-cue associations. In the nucleus, HDAC5 represses numerous target genes, but HDAC5's intrinsic deacetylase activity is much lower than class I HDACs leading some to propose that class IIa HDACs, like HDAC5, function largely as protein scaffolds for recruitment of class I HDACs, like HDAC3, to genomic sites. Using tandem mass spectrometry, we observed that two conserved cysteines within HDAC5's enzymatic domain form an intramolecular disulfide bond in vitro and in vivo. Mutation of these cysteines abolishes HDAC5 deacetylase activity without disrupting HDAC3 binding or altering HDAC5 subcellular localization. Unlike enzyme-active nuclear HDAC5, viral-mediated expression of the deacetylase-dead HDAC5 in the adult rat NAc fails to reduce cue-induced cocaine seeking following self-administration. Moreover, it fails to reduce NAc

medium spiny neuron intrinsic excitability, a recently identified candidate mechanism by which HDAC5 limits drug-cue memory formation or stability. These data support a novel role for the intrinsic enzymatic activity of HDAC5 in decreasing relapse-like behavior, possibly through the modulation of chromatin structure and expression of genes linked to intrinsic excitability.

Disclosures: D.J. Wood: None. **E. Tsvetkov:** None. **S. Comte-Walters:** None. **L. Ball:** None. **E.M. Anderson:** None. **M. Taniguchi:** None. **C. Cowan:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.08/MM14

Topic: G.09. Drugs of Abuse and Addiction

Support: Pathway to Independence Award (R00DA045795, PJH)
Center of Excellence Grant Program (P30DA033934, PJH)

Title: Reprogramming transcription factor function regulates drug specific behavioral responses and transcription

Authors: *J. A. PICONE[1], R. K. KIM[2], D. P. LIRA[2], G. M. SILVA[2], N. L. TRUBY[2], X. CUI[2], P. J. HAMILTON[2];
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Abstract: Reprogramming transcription factor function regulates drug specific behavioral responses and transcriptionAuthors*J.A. Picone, K. Kim, D.P. Lira, G.M. Silva, N.L. Truby, X. Cui, P.J. Hamilton; Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine., Richmond, VA**DisclosureJ.A. Picone:** None. K. Kim: None. D.P. Lira: None. G.M. Silva: None. N.L. Truby: None. X. Cui: None. P.J. Hamilton: None**Abstract**Understanding the molecular substrates of the stages of drug addiction may allow for the design of pharmacotherapies that block or reverse key events of the progression of drug addiction. *Zfp189* is a CREB-target gene which itself encodes an unstudied nucleus accumbens (NAc) neuronal transcription factor that has been demonstrated to regulate transcriptional adaptations following drug- or stress-experience. Published data reveals that using the CRISPR/dCas9-mediated CREB delivery to the *Zfp189* CRE site increases *Zfp189* mRNA levels in the NAc and decreases reward associations for mild doses of cocaine. To further examine the downstream relationship between ZFP189 and physiological response to saline, cocaine, and morphine, three reprogrammed synthetic ZFP189 transcription factors were used to study drug-induced behavior and transcription. Three ZFP189 variants used were: $ZFP189^{WT}$, $ZFP189^{NFD}$, and $ZFP189^{VPR}$. Mice received one of these ZFP variants to the NAc via viral-mediated gene transfer. We then performed a drug locomotor sensitization assay with saline, cocaine, or morphine. In response to cocaine treatment, mice with $ZFP189^{VPR}$ intra-NAc moved significantly more than the

$ZFP189^{WT}$ group. More interestingly, this increased locomotion is unique to cocaine experience, as there is no difference in locomotor activity between the ZFP189 variant groups in response to saline or morphine administration. We performed cocaine intravenous administration and observed significant changes in rates of cocaine seeking behaviors between the ZFP189 TFs, immediately following surgery and after a period of forced abstinence. RNA sequencing of manipulated NAc tissues from these mice revealed that the differences in behavioral response to cocaine across the variant groups coincided with transcriptional changes. Specifically, $ZFP189^{VPR}$ was only able to regulate NAc transcription in mice that had been treated with cocaine. These results suggest ZFP189 specifically drives cocaine-induced transcription and behaviors.

Disclosures: **J.A. Picone:** None. **R.K. Kim:** None. **D.P. Lira:** None. **G.M. Silva:** None. **N.L. Truby:** None. **X. Cui:** None. **P.J. Hamilton:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.09/MM15

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant P50DA037844

Title: Genome-wide association study identifies loci influencing initial drug-taking and cocaine induced locomotion

Authors: *N. K. AMISSAH[1], C. P. KING[1,2], B. M. THOMPSON[1], E. A. RAKOWSKI[1], L. T. HANNAN[1], A. CHITRE[3], O. POLESSKAYA[3], H. CHEN[4], L. C. SOLBERG WOODS[5], A. A. PALMER[3], T. SANCHES[3], B. PENG[3], P. J. MEYER[1];
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Abstract: Addiction vulnerability is influenced by multiple factors, including initial drug-sensitivity, acquisition of drug-taking, and escalation of intake. However, the genetic underpinnings of these factors are difficult to study due to the complex nature of human environments. To overcome these difficulties, we performed a genome wide association study on intermittent cocaine self-administration (IntA) in rats. Genotypically and phenotypically diverse male and female heterogenous stock (HS) rats (n= 446) were assessed for multiple measures of drug-directed behavior, including cue seeking, acquisition of drug use, progressive ratio responding and reinstatement of drug use. We found that rats significantly escalated cocaine intake and motivation during IntA cocaine self-administration, with females having higher levels

of initiation and progressive ratio responding. Genetic analyses indicated that acquisition of drug-taking (h^2 =.331) had the highest heritability, with other traits such as drug-induced locomotion during IntA and lifetime intake having moderate heritability estimates as well (h^2 = .249-.276). Further analyses have identified seven quantitative trait loci (QTL) so far: three of which were associated with initial acquisition of drug-taking and the locomotor response to cocaine. Both acquisition and cocaine-induced locomotion were influenced by a locus on chromosome 13 that included a regulator of G protein signaling (*Rgs7*), which contained a coding variant predicted to impact protein function, and had previously been implicated in cocaine and opioid responses. Expression QTL analysis also revealed that these loci influenced the expression of other genes in these regions (e.g. *Cnst*, *Kif28p*, and *Cdc42bpa*). Ongoing work includes increasing sample size in order to increase power to detect loci associated with other heritable measures of cocaine self-administration, including IntA escalation of intake and progressive ratio responding. In conclusion, these studies show that HS rats is a good model for detecting genes associated with complex traits related to cocaine use disorder.

Disclosures: **N.K. Amissah:** None. **C.P. King:** None. **B.M. Thompson:** None. **E.A. Rakowski:** None. **L.T. Hannan:** None. **A. Chitre:** None. **O. Polesskaya:** None. **H. Chen:** None. **L.C. Solberg Woods:** None. **A.A. Palmer:** None. **T. Sanches:** None. **B. Peng:** None. **P.J. Meyer:** None.

Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR103.10/MM16

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA T32 DA007288
NIDA R01 DA032708
NIDA P50 DA046373

Title: Npas4 and parvalbumin fast-spiking interneurons in the nucleus accumbens: molecular mechanisms of drug-related behavior

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Abstract: Substance use disorders (SUDs) are characterized in part by a vulnerability to relapse which persists even after prolonged periods of abstinence. Associations between drug reward and environmental cues are a fundamental component of this vulnerability, often triggering a return

to drug-seeking behavior. Expression of Neuronal PAS Domain Protein 4 (NPAS4), an activity regulated transcription factor, is induced following cocaine conditioning in a select ensemble of cells within the nucleus accumbens (NAc), a brain region heavily implicated in the early reinforcing effects of drugs of abuse and drug-seeking behavior. This ensemble is composed primarily of medium spiny neurons (MSNs; ~76%) but also contains a smaller population of other striatal cell types (~24%), including parvalbumin-positive fast-spiking interneurons (PV-FSIs). Previous work in our lab has shown that Gi-DREADD-mediated inhibition of this ensemble significantly decreases cocaine conditioned place preference (CPP) and identifies a role for NPAS4 in regulating cocaine-induced shifts in the D1-MSN:D2-MSN activation balance, ultimately facilitating the formation of drug-cue associations and promoting drug-seeking behavior. PV-FSIs make up just 1-2% of the total neuronal population in the NAc, but account for a significant portion of the GABAergic inhibitory input underlying basal MSN activity levels and have themselves been implicated in facilitating drug-related behavior. We show here that loss of NPAS4 specifically in NAc PV-FSIs significantly decreases cocaine CPP, while having no effect on cocaine-induced locomotor sensitization, suggesting that NPAS4 may facilitate the formation of drug-cue associations via its function in this cell type. Ongoing work in our lab is investigating whether this function extends to facilitate other drug-related behavior, including cue-induced reinstatement of drug self-administration. We are also working to identify the underlying mechanisms by which NPAS4 in PV-FSIs facilitates these behaviors, exploring how loss of NPAS4 in this cell type influences PV-FSI and neighboring MSN activity during various phases of drug exposure and drug seeking.

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Poster

PSTR103. Addictive Substances: Regulation of Neural Function and Behavior

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NIH grant F30MH115536

Title: Cyclic AMP-mediated homeostatic regulation of HCN channels in VTA dopamine neurons promotes cocaine reinforcement

Authors: *X. LIU[1], L. MU[2], C. R. VICKSTROM[3], V. FRIEDMAN[4], T. KELLY[3], Y. HU[3], J. R. MANTSCH[3], Q.-S. LIU[3];
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Abstract: Chronic cocaine exposure induces enduring neuroadaptations that facilitate motivated drug taking. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are known to modulate neuronal firing and pacemaker activity in ventral tegmental area (VTA) dopamine neurons. However, it remained unknown whether cocaine self-administration affects HCN channel function and whether HCN channel activity modulates motivated drug taking. We report that rat VTA dopamine neurons predominantly expressed *Hcn3-4* mRNA, while VTA GABA neurons expressed *Hcn1-4* mRNA. Both neuronal types displayed similar hyperpolarization-activated currents (I_h), which were facilitated by acute increases in cAMP. Acute cocaine application decreased voltage-dependent activation of I_h in VTA dopamine neurons, but not in GABA neurons. Unexpectedly, chronic cocaine self-administration resulted in enhanced I_h selectively in VTA dopamine neurons. This differential modulation of I_h currents is likely mediated by a D_2 autoreceptor-induced decrease in cAMP as D_2 (*Drd2*) mRNA is predominantly expressed in dopamine neurons, and chronic stimulation of Gi-DREADD in VTA dopamine neurons was sufficient to enhance I_h. Thus, cocaine self-administration induces homeostatic upregulation of HCN function via chronic decreases in cAMP. A leading cause of death in long-term cocaine users is dilated cardiomyopathy-associated heart failure. We show that systemic injection and intra-VTA infusion of the HCN blocker ivabradine, an FDA-approved drug for the treatment of heart failure, reduced cocaine self-administration under a progressive ratio schedule and produced a downward shift of the cocaine dose-response curve. Our results suggest that HCN blockers could be a multifaceted tool for the treatment of cocaine use disorder.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.01/MM18

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01EB031765
NIH Grant P30DA048742

Title: Nonhuman primates as a translational model of chronic cocaine use

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Abstract: Addiction is characterized by compulsive drug seeking and taking. A better understanding of the neurobiological changes associated with different stages of addiction is

required to identify biomarkers linked to risk of onset, maintenance, and relapse. However, it is difficult if not impossible to collect human data from pre-drug, initial use, addiction, to abstinence and relapse. Therefore, the causes and consequences of chronic drug use are often confounded in human work. Animal models allow for tracking within-subject changes from pre-drug through the stages of developing an addiction. Nonhuman primates (NHP) offer distinct characteristics as a model of human drug use; the phylogenetic proximity results in similar brain organization and function, drug pharmacokinetic and pharmacodynamic profiles to humans. Here, we employed an intermittent self-administration (SA) paradigm in which NHPs voluntarily trigger drug delivery, which is similar to human voluntary drug consumption. Four macaque monkeys self administered cocaine for 100 days. We employed a within-subject longitudinal design, acquiring resting state fMRI data at 9 time points: 2 pre-drug baselines; after 5, 45 and 95 days of cocaine SA; after 5, 30 and 60 days of abstinence; and relapse. We focused our analysis on the reward system, a network of brain regions primarily involved in processing incentive value. Previous neuroimaging studies in humans have indicated that this system is hyper-engaged in individuals with substance use disorder, which is positively correlated with craving, addiction severity, and use duration. Here we wanted to directly test the hypothesis that this up-regulation of the reward system is drug-induced. Notably, we used resting-state functional connectivity (rs-FC) which measures the temporal correlation of spontaneous hemodynamic signals among spatially distributed brain regions. Results demonstrated that rs-FC within the reward network increased during the first 45 days and then decreased during the second 45 days of drug SA. These results suggest that drug-use is initially driven by sensitization of the reward system, but that tolerance plays an increasingly larger role over time. Interestingly, the rs-FC of the reward system increased again after 5 days of abstinence. This heightened connectivity during early abstinence may mediate the increased salience of drug cues and their potential to trigger relapse. In sum, we provide evidence that cocaine-induced alterations in brain function are dependent on the time point at which the data is acquired. In particular, we demonstrate that the reward system is dynamically changing throughout addiction and abstinence.

Disclosures: **A.M.G. Manea:** None. **J. Zimmermann:** None. **A. Zilverstand:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA052169 to JRM and MCH
E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals

Title: Investigating sex and reproductive phase differences in drug-seeking behavior following ERβ antagonism in the prelimbic prefrontal cortex

Authors: *B. SCHULTZ[1], D. B. NOWAK[1], M. E. MORRISSEY[1], M. C. HEARING[2], J. R. MANTSCH[1];
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Abstract: Substance use disorders (SUDs) are among society's most prevalent challenges and cause harm to millions annually. Effective treatments for SUDs are lacking; thus, further research is needed to understand unique factors, such as biological sex, that contribute to the chronic course of SUDs. Relapse is a barrier to abstinence for patients with SUDs; moreover, data from clinical populations show that biological sex plays a role in relapse susceptibility. Females tend to face more challenges abstaining and have a higher relapse incidence than males while also showing females respond better to interventions compared to males. Preclinical studies suggest that these differences are mediated in part by circulating gonadal hormones such as 17β-estradiol (E2). We have implicated the prelimbic prefrontal cortex (PrL-PFC) as a site of E2 regulation of drug seeking behavior in ovariectomized (OVX) female rats. We found that antagonism of estrogen receptor beta (ERβ) and G-protein coupled estrogen receptor (GPER) but not ERα in the PrL-PFC attenuates E2-potentiated cocaine-primed reinstatement following intravenous cocaine self-administration and extinction. Based on these observations, we hypothesize that E2 actions at ERβ and GPER in the PrL-PFC underlie sex- and reproductive phase-dependent differences in cocaine-primed reinstatement. To test this hypothesis, we bilaterally micro-infused the selective ERβ antagonist, PHTPP (2.12ng/0.3ml/side) or the selective GPER antagonist, G15 (7.5ng/0.3ul/side) into the PL-PFC prior to testing for cocaine-primed reinstatement (doses) in adult male and age-matched freely cycling, gonadally intact female rats following cocaine self-administration and extinction. Estrous cycle phase was assessed in each female rat via cytological assessment of vaginal smears. Intra-PFC PHTPP failed to alter cocaine seeking in males. While, overall, intra-PFC PHTPP also did not alter reinstatement in females, estrous phase-specific effects of PHTPP were observed. Intra-PFC PHTPP attenuated drug seeking behavior in females tested during proestrus (high E2) but not during metestrus, diestrus, or estrus. These findings align with previously published results gathered from OVX females pretreated with exogenous E2 at proestrus levels. Ongoing studies are being conducted to confirm these results and examine the effects of GPER antagonism in the PL-PFC on both male and female drug seeking behavior. Further understanding of sex differences in SUD may lead to targeted therapeutic interventions that are effective in reducing relapse susceptibility during a period of abstinence.

Disclosures: B. Schultz: None. **D.B. Nowak:** None. **M.E. Morrissey:** None. **M.C. Hearing:** None. **J.R. Mantsch:** Other; E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

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Topic: G.09. Drugs of Abuse and Addiction

Support: "Progetti per avvio alla ricerca Tipo 1" grant AR1221816C636292

Title: Oxytocinergic system alteration induced by attachment bond disruption mediates the vulnerability to cocaine effects in adulthood

Authors: *D. MUNICCHI[1], C. MANCINI[2], S. L. D'ADDARIO[3], A. PASSERI[1], M. TIBERI[3], L. BABICOLA[3], M. DI SEGNI[1], L. LO IACONO[3], D. ANDOLINA[1], C. CIFANI[2], V. CHIURCHIU[3], R. VENTURA[1];
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Abstract: Early life experiences have the potential role to alter both brain development and adult behavior. Particularly, the formation of the attachment bond is crucial for well-being and mental health, and its disruption is related to expression of several psychopathologies, such as drug addiction. Interestingly, oxytocin (Oxt) plays an important role in the formation of the attachment bond and dopaminergic (DA) circuits development, and alterations of both Oxt and DA systems are involved in drug addiction. We have recently showed that an early life manipulation (Repeated Cross Fostering, RCF) able to alter the mother-pups bond induces in C57 female mice a behavioral phenotype characterized by increased vulnerability to cocaine effects in adulthood affecting DA mesocorticolimbic system. Here, we hypothesize that RCF manipulation impacts Oxt system development increasing the vulnerability to cocaine effects in adult life. To test this hypothesis, we investigated the main targets of the Oxt system: Oxt levels, Oxt receptor (OxtR) within the mesocorticolimbic system and the Receptors for Advanced Glycation End-Products (RAGE) (a recently identified Oxt transporter), across different cellular subtypes in pFC. We found that RCF manipulation induced a reduction in both Oxt and OxtR levels in the brain of female C57 mice at postnatal day (PND) 5. Moreover, in adult RCF compared to Control females, altered OxtR levels and Oxt release in the nucleus accumbens (NAc) induced by acute cocaine injection were also observed. Finally, we also reported reduced RAGE expression in specific cellular subtypes. Restoring brain oxytocin levels through subcutaneous injection of oxytocin (20ul, 0.2 ng/ul) from PND1 to PND4, was sufficient to reduce increased sensitivity to cocaine effects in adult RCF females (as evaluated by cocaine-induced Conditioned Place Preference) and normalize both Oxt and OxtR levels in adulthood. Altogether, our results demonstrate the critical role for Oxt system in RCF-induced vulnerability to cocaine effects reported in adult C57 females.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH/NIDA grant R00DA039991

Title: The potential role of the Edinger-Westphal nucleus during context associated cocaine seeking in rat.

Authors: *N. M. HINDS, I. D. WOJTAS, D. M. PULLEY, S. J. MCDONALD, D. F. MANVICH;
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Abstract: The Edinger-Westphal nucleus (EW) is a small neuronal population located next to the oculomotor nucleus and the midbrain periaqueductal gray (PAG) and is typically associated with oculomotor function. However more recent evidence suggests the EW is more complex, with two distinct neuronal subpopulations; the preganglionic population (EWpg) which is involved in sending parasympathetic signals towards the eye and the centrally projecting population (EWcp) that is recruited during stress adaptation, anxiety, and pain. In addition, the EWcp has also been shown to be activated in response to administration of drugs of abuse like alcohol, opioids, barbiturates, and psychostimulants but whether it is engaged during drug-seeking episodes has yet to be identified. Thus, this study aimed to determine if the EW may be involved in cocaine-seeking induced by a context cue associated with cocaine availability, social and nonsocial stress, or a saline social stress event. To do this, adult male and female Long-Evans rats were trained to self-administer cocaine (0.5 mg/kg/inf, i.v.) or saline in 2-h daily sessions for 20 d. On days 11, 14, 17, and 20, a discrete tactile cue was present in the operant chamber, and these sessions were immediately followed by social defeat stress **(SDS; n=16, 8/sex),** nonsocial footshock stress **(FS; n=12, 6/sex),** no-stress control **(n=12, 6/sex)** and a social stress saline control (**Sal-SDS**; n=5, 3M, 2F)**.** Beginning on day 21, animals underwent extinction training during which lever-presses were not reinforced. Once extinguished, rats were re-exposed to the tactile cue singaling their assigned stress/no-stress stimulus and reinstatement of cocaine or saline seeking was measured for 2 h under extinction conditions. Immediately after the reinstatement test, animals were sacrificed, and brains collected and processed for c-Fos expression via immunohistochemistry where an association between EWcp Fos expression in cocaine seeking groups as compared to the saline control (p=0.08) was found. Furthermore, Fos activation across all cocaine seeking groups together was significantly and positively correlated with cocaine seeking magnitude regardless of stress history. Specifically in the SDS group, the EWcp correlated with active coping behaviors during social stress events as well as activity in other brain regions measured by Fos expression like the lateral and ventrolateral PAG, bed nucleus of the stria terminals and the prelimbic prefrontal cortex. Taken together, this data supports the current literature suggesting a potential role of the EWcp in drug seeking with future studies aimed at determining if it plays a causal role in these behaviors.

Disclosures: N.M. Hinds: None. **I.D. Wojtas:** None. **D.M. Pulley:** None. **S.J. McDonald:** None. **D.F. Manvich:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA-049139
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Title: Optogenetic inhibition of infralimbic projections to the nucleus accumbens shell and amygdala impairs the extinction of cocaine-seeking behavior in rats

Authors: *A. ZIMBELMAN[1], K. E. NETT[4], M. S. MCGREGOR[2], V. ALIZO VERA[5], M. R. HARRIS[1], R. T. LALUMIERE[1,2,3];
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Abstract: Previous findings indicate that the infralimbic cortex (IL) regulates the extinction of cocaine seeking in rats. Our ongoing research has used activity-controlled optogenetic procedures to delineate the neural pathways from the IL involved in such extinction, specifically focusing on IL projections to the nucleus accumbens shell (NAshell) and amygdala. To investigate these pathways, female and male Sprague-Dawley rats received bilateral microinjections of AAV-CaMKII-eArchT3.0 or eYFP-control into the IL, bilateral fiber optics targeted at the NAshell or amygdala, and implantation of an intrajugular catheter. Rats then underwent at least 12 d of cocaine self-administration (2 h/d), in which an active lever press produced a cocaine infusion (~0.33 mg/kg/infusion) paired with light/tone cues. Rats then underwent 5 d of shortened (30 min) extinction training sessions, during which an active lever press resulted in no cocaine infusion or cues and triggered 20 s of illumination (561 nm) of IL terminals in the NAshell or amygdala. As a measure of extinction learning retention, all rats then underwent 7 d of full-length (2 h) extinction sessions without inhibition. Results indicate that IL-NAshell inhibition immediately following an unreinforced lever press increased lever pressing during extinction training and impaired the retention of extinction learning, as assessed during subsequent extinction sessions without optical inhibition. IL-amygdala inhibition immediately following an unreinforced lever press had no effect on active lever presses during the extinction sessions with inhibition but impaired extinction retention during subsequent sessions without inhibition. Critical encoding of extinction learning does not appear to extend beyond the initial 20 s post-lever press period, as delayed IL-NAshell and IL-amygdala inhibition had no effect on extinction learning. Similar patterns of results were observed in male and female rats in all experiments. Ongoing experiments are further examining the circuitry involved in cocaine extinction learning, focusing on input to the IL. In these experiments, optogenetic inhibition is given to basolateral amygdala terminals in the IL, following the same behavioral approach outlined above. Overall, these findings further elucidate the neural mechanisms, centered around the IL, that are involved in the encoding of cocaine extinction contingencies.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Title: Increasing cognitive flexibility to reduce compulsive drug use and inflexible drug seeking

Authors: *D. M. BORTZ, M. M. TORREGROSSA;
Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Compulsive drug taking is a hallmark of substance use disorders (SUDs) and is characterized by context or cue-driven inflexible drug-seeking behaviors. Although cognitive flexibility, as measured by cognitive batteries, is distinct from the inflexibility that drives habitual drug seeking, there are data that suggest the two are related. Strategy/set switching or reversal learning performance is impaired *after use* of substances like alcohol, methamphetamine or cocaine. Structural and behavioral indices of cognitive flexibility impairments also *predict* substance abuse across species. If cognitive inflexibility can predict substance abuse across species, we propose that increasing flexibility might reduce compulsive drug use and reduce relapse. We hypothesized that activating a pathway from the medial prefrontal cortex to the medial septum (mPFC-MS), which improves cognitive flexibility, could be a means to reduce relapse-related behaviors in a SUD-model context. To test this, male and female rats were trained to self-administer (SA) cocaine using a reinforcement schedule that is cue extinction-resistant (second-order-SO), one that remains goal-directed (fixed-ratio-FR), or saline, while also learning to discriminate between nose-poke ports in an operant chamber for a pellet reward. After 10 days of discrimination training, rats underwent a strategy-switching test where they had to inhibit the previously learned strategy and learn a previously ignored strategy. Strategy switching was measured in mPFC-MS activated (designer receptors exclusively activated by designer drugs) vs. control rats across all three cocaine conditions. Dopamine (DA) and glutamate (GLUT) release was measured in dorsal striatum (fiber photometry) during training and strategy switching. Following the conclusion of the cognitive behavior, we measured compulsive drug taking, as well as cocaine seeking before cue extinction, after cue extinction, and after 2 periods of abstinence. Dorsal striatum DA and GLUT release, and the above behaviors, were compared in mPFC-MS activated vs. control rats. We found that SO-trained rats demonstrated impaired strategy switching compared to FR and saline rats. Activation of the mPFC-MS pathway improved strategy-switching performance in all groups compared to controls from the same cocaine SA category. The improvement in strategy switching was associated with a reduction in dorsal striatal DA release at trial onset. Activation of the mPFC-MS pathway also reduced cocaine seeking after extinction compared to controls within the same category. This difference was particularly distinct in SO rats when tested after abstinence.

Disclosures: **D.M. Bortz:** None. **M.M. Torregrossa:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals. CJH has equity in Formulate Biosciences, Inc.

Title: Involvement of Gq signaling in 2-arachidonoyglycerol-dependent effects of corticosterone on inhibitory transmission in the prelimbic cortex and cocaine-seeking behavior

Authors: *L. J. LASKOWSKI[1], D. R. OLIVEIRA[1], E. M. DONCHECK[2], J. MCREYNOLDS[3], B. WINDSOR[1], X. LIU[1], G. SAUBER[1], G. PEREZ[1], M. ESTES[1], B. E. SCHULTZ[1], Q.-S. LIU[1], C. J. HILLARD[1], J. R. MANTSCH[1];
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Abstract: During stress, corticosterone (CORT) can promote cocaine seeking by increasing excitability of pyramidal neurons projecting from the prelimbic prefrontal cortex (PrL-PFC) to the nucleus accumbens. We have shown that endocannabinoid signaling couples glucocorticoids to synaptic effects in the PFC, specifically increasing the synthesis of 2-arachidonoylglycerol (2-AG). Through this mechanism, CORT rapidly decreases GABAergic transmission via 2-AG activation of presynaptic cannabinoid 1 receptors (CB1Rs) on GABA interneurons. However, the mechanisms through which CORT mobilizes 2-AG in PFC pyramidal neurons are unknown. Earlier results indicate that the effects of CORT are not blocked by PrL-PFC micro-infusions of the glucocorticoid receptor (GR) antagonist, RU486, or AAV-Cre knockdown of PrL-PFC GR in GR "floxed" rats and are mimicked by membrane impermeable bovine serum albumin-conjugated CORT (BSA-CORT). Together, these data indicate that CORT acts through a rapid non-GR, membrane delineated process to induce the synthesis of 2-AG. Here we demonstrate that PrL-PFC micro-infusions of the diacylglycerol lipase (DAGL) inhibitor DO34 prevent CORT-potentiation of reinstatement by a low-dose priming injection of cocaine following self-administration/extinction in male rats. DO34 application prevents CORT-induced reductions in miniature inhibitory postsynaptic currents (mIPSC) frequency in layer V PrL-PFC pyramidal neurons assessed using whole-cell recording in rat brain slices. We hypothesized that Gq GPCR-dependent production of the DAGL substrate diacylglycerol mediates 2-AG synthesis and examined the effects of a palmitoylated peptide targeting the Gαq-binding domain of GPCRs. PrL-PFC micro-infusions of the palpeptide prevented reinstatement potentiated by CORT but not

the CB1R agonist, WIN55,212-2, and blocked CORT induced reductions in mIPSC frequency. Ongoing experiments are investigating the effects of the selective macrocyclic depsipeptide Gq inhibitor, FR900359, on CORT-potentiated cocaine seeking and CORT reductions of inhibitory transmission in the PrL-PFC. Finally, we will provide an update on continuing experiments using BRET-based screening in transfected cells to identify potential Gq-coupled receptors that are CORT-sensitive. Altogether, these findings suggest that CORT can engage Gq signaling mechanism in the PrL-PFC to mobilize endocannabinoid signaling, attenuate inhibitory transmission, and promote excitability of projection pathways that contribute to drug seeking.

Disclosures: **L.J. Laskowski:** None. **D.R. Oliveira:** None. **E.M. Doncheck:** None. **J. McReynolds:** None. **B. Windsor:** None. **X. Liu:** None. **G. Sauber:** None. **G. Perez:** None. **M. Estes:** None. **B.E. Schultz:** None. **Q. Liu:** None. **C.J. Hillard:** None. **J.R. Mantsch:** Other; E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.08/MM25

Topic: G.09. Drugs of Abuse and Addiction

Support: DA031900
NSF GRFP

Title: Hypocretin receptor 1 blockade on motivation for cocaine and dopamine transmission in the nucleus accumbens core

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Abstract: Relapse to cocaine use after periods of abstinence remains one of the greatest obstacles in treating cocaine use disorder. Although the factors that contribute to relapse have not been fully defined, accumulating evidence suggests that adaptations in mesolimbic dopamine systems that occur during abstinence may contribute to cocaine craving and propensity for relapse. Unfortunately, pharmacological approaches that target dopamine systems directly, are largely ineffective or intolerable and may pose abuse potential themselves. Therefore, identifying novel treatments for cocaine use disorder remains a critical research objective. The hypocretin/orexin neuropeptide system has been shown to regulate dopamine transmission and cocaine-associated behavior. Our previous studies show that treatment with the hypocretin receptor 1 antagonist, RTIOX-276, 30 minutes before assessment reduces motivation for cocaine and attenuates the effects of cocaine on dopamine transmission. Notably, the effects of RTIOX-276 on dopamine transmission are maintained for at least 24 hours suggesting a lasting effects of hypocretin receptor 1 blockade. In the present study, we tested the hypothesis that a single

treatment with RTIOX-276 can reduce motivation for cocaine following a period of abstinence and produce lasting alterations in dopamine transmission. Rats were first pre-assessed for cocaine consumption and demand using the within-session threshold schedule where the unit dose of cocaine is reduced over the course of individual self-administration sessions. Following this pre-assessment, rats self-administered cocaine on an intermittent access schedule for 7 days to promote dopamine adaptations that occur after intermittent exposure to cocaine. After intermittent access exposure, rats were treated with vehicle or RTIOX-276 on the first day of a 7-day abstinence period. After abstinence, rats underwent either a post-assessment of cocaine consumption and demand or examination of dopamine transmission in the nucleus accumbens core. We found that a single dose of RTIOX-276 on the first day of abstinence reduced demand for cocaine 7 days later, without affecting consumption. Furthermore, using fast scan cyclic voltammetry we found that RTIOX-276 normalized aspects of dopamine transmission following intermittent access to cocaine. These observations suggest that RTIOX-276 may be a beneficial treatment for cocaine use disorder by reducing demand for cocaine through downstream alterations in dopamine terminals in the nucleus accumbens.

Disclosures: S.B. Samels: None. **P.J. Clark:** None. **J.K. Shaw:** None. **R.A. España:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA049930
OHSU Startup Funds
F32 DA050457
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NRSA F31DA057063

Title: Dopamine signaling in nucleus accumbens core contributes to incubation of cocaine craving

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Abstract: Relapse represents a consistent clinical problem when treating individuals with substance use disorder. We and others have studied this in rodents using the incubation of cocaine craving model. In this model, rats begin by learning to nose poke to receive IV cocaine

(6 h/d x 10 d; infusion paired with light cue). After this regimen of self-administration, they enter a period of prolonged abstinence during which cue-induced cocaine seeking progressively intensifies and then remains high for months. Previous work has shown that expression of incubation depends on strengthening of AMPAR transmission in the nucleus accumbens core (NAcc). However, despite the importance of NAcc dopamine (DA) for motivated behavior, little is known about its role in incubation. We investigated this in male (M) and female (F) rats using DA biosensors and pharmacology. For Study 1, prior to drug SA, GRAB-DA2m was expressed in NAcc and a fiber optic cannula was implanted. Dopamine transients were then recorded during cue-induced seeking tests on forced abstinence day (FAD) 1 (before incubation) and FAD40-50 (after incubation). Photometry recordings during cue-induced seeking tests demonstrated DA transients time-locked to nose pokes in the previously active hole on both FAD1 and FAD40-50 ($p < 0.0001$; n = 23, 9 M/14 F, within subject design). The magnitude of the response (AUC) did not differ between FAD1 and FAD40-50 ($p = 0.5090$). Meanwhile, in Study 2 we implanted guide cannulas for intra-NAcc infusion of DA antagonists prior to SA. The D1 DA receptor antagonist SCH39166 (1µg/0.5µL/hemisphere) or vehicle was infused in NAcc 15 min prior to the FAD40-50 seeking test (between subject design). Expression of incubation was significantly reduced by SCH39166 (n = 17, 7 M/10 F) vs. vehicle (n = 13, 7 M/6 F), with a more pronounced effect in males (post hoc tests: M/F, $p = 0.0005$; M, $p = 0.0004$; F, $p = 0.0549$). D2 antagonist studies are underway and preliminary results indicate D2 antagonism via L-741,626 (1µg/0.5µL/hemisphere) also reduces incubated cocaine seeking. In conclusion, cue-induced cocaine seeking is accompanied by a similar magnitude of NAcc DA release in early and late abstinence, suggesting that 'incubated' seeking may not reflect enhancement of DA release (i.e., a presynaptic effect). It is possible that 'incubated' seeking depends on postsynaptic enhancement of DA signaling, as well as on postsynaptic strengthening of AMPAR transmission (demonstrated previously). Future studies will examine how DA and glutamate interact to set the gain on cue reactivity during cocaine abstinence.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.10/NN2

Topic:

Support: P30 DA029925
F32 DA043931
K99/R00 DA048970

Title: Beta-arrestin2 deletion in d2 cells selectively impairs cocaine self-administration

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Abstract: The dopamine D1 and D2 receptors are G protein-coupled receptors that mediate drug reward and behavioral reinforcement largely via actions originating from mutually exclusive cell populations. D1 and D2 signaling is shaped by the regulatory protein β-arrestin2; however, the role of β-arrestin2 in dopamine-related drug-taking and -seeking behaviors remain to be fully analyzed. We recently established multi-stage intravenous self-administration (IVSA) paradigms in mice for the psychostimulant cocaine and the short-acting opioid remifentanil. We used these paradigms to assess the effect of cell-type-specific deletion of β-arrestin2 on drug-taking and -seeking behaviors. These responses were assessed in mice lacking β-arrestin2 either in D1-expressing neurons ($D1^{\beta arr2\ KO}$) or in D2-expressing neurons ($D2^{\beta arr2\ KO}$) and compared to their wild-type (WT) littermate controls. Genotypes were age- and sex-matched. Mice with indwelling jugular catheters were trained in operant chambers to self-administer cocaine or remifentanil, paired with a cue light, by lever responding. Mice completed active *vs.* inactive lever discrimination training at FR1, FR2 and FR4, as dictated by a contingent advancement study protocol. Once acquired, IVSA was assessed at 5 cocaine or 6 remifentanil doses. Dose-response testing was followed by extinction sessions in which cues were withheld and lever responses had no programmed consequences. Following extinction, mice underwent a cue-induced reinstatement session in which drug-associated cues were presented without drug reinforcement. We found that cocaine- and remifentanil-associated lever responding was acquired, extinguished, and reinstated in all genotypes. In the cocaine paradigm, $D2^{\beta arr2\ KO}$ mice showed a trend toward increased time to train, they self-administered less cocaine at low-moderate doses, and exhibited increased latency to initiate lever responding compared to WT controls. $D2^{\beta arr2\ KO}$ mice performed comparably to controls in cocaine extinction and reinstatement sessions. In contrast, performance in $D1^{\beta arr2\ KO}$ mice was similar to that of WT mice at all stages of cocaine IVSA. In the remifentanil paradigm, neither $D1^{\beta arr2\ KO}$ nor $D2^{\beta arr2\ KO}$ mice were distinguished from controls at any stage. Despite changes in cocaine taking, $D2^{\beta arr2\ KO}$ mice displayed intact sucrose preference. These findings suggest that β-arrestin2 regulates drug IVSA through a cell type- and drug class-specific mechanism. These findings indicate that cellular mechanisms driving reinforcement differ by drug class and they identify β-arrestin2 in D2-expressing cells as a potential target for stimulant use disorder.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.11/NN3

Topic: G.09. Drugs of Abuse and Addiction

Support: DA031900
NIH-NINDS R44NS117201

Title: G-protein biased activation of D3 receptors disrupts dopamine dynamics in the nucleus accumbens

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Abstract: While presynaptic D2 receptors (D2R) influence on NAc DA dynamics is well characterized, the importance of D3 receptors (D3R) is far less understood given the lack of D3R-selective agonists. We recently demonstrated that SK609 is a selective and G-protein biased (GPB) agonist of D3R and promotes short-term activation of ERK1/2. By comparison, the well characterized D3R-preferring agonist Pramipexole (PRX) is an unbiased agonist and induces short and long-term activation of ERK1/2. Similar to D2R, prior studies have demonstrated interactions between the D3R and membrane-bound dopamine transporter (DAT). ERK1/2 phosphorylates DAT at Thr53 (pDAT) which sensitizes DAT to the effects of cocaine. Therefore, we hypothesized that activation of D3R by GPB agonists may counteract DAT sensitization by temporally limiting activation of ERK1/2 and subsequently reducing pDAT expression. In this study, we examined the effects of SK609 on DAT phosphorylation and function and compared these effects to those following PRX treatment. Additionally, we examined the effects of SK609 and PRX on cue-induced cocaine seeking behavior. First, we assessed the temporal activation profile of ERK1/2 and pDAT expression following either SK609 or PRX alone and after pre-treatment with cocaine on SH-SY5Y cells overexpressing D3R. Next, we performed *ex vivo* fast scan cyclic voltammetry (FSCV) in the NAc core of naive rats to examine the effects of SK609 and PRX on DAT sensitivity to cocaine. Finally, we assessed the effects of acutely administered SK609 or PRX on cue-induced seeking after a forced abstinence period from intermittent access to cocaine. We determined that SK609 treatment did not increase pDAT expression when cells were pre-treated with cocaine, while PRX significantly increased pDAT expression with cocaine pre-treatment. Further, we found that both SK609 and PRX reduced dopamine release. With respect to cocaine seeking behavior, both SK609 and PRX reduced cocaine seeking, although SK609 did so to a greater extent. Together, these studies reveal that SK609 attenuated DAT sensitization and subsequent cocaine seeking behavior, likely through its GPB signaling effects through D3R that temporally limits the availability of pDAT. Conversely, PRX activated D3R signaling through both β-arrestin and Gi-coupled recruitment and was less effective at attenuating DAT sensitization to cocaine.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.12/NN4

Topic: G.09. Drugs of Abuse and Addiction

Support: DA052385
DA043443
DA041480

Title: The role of negative prediction error and VTA to NAc circuits in the destabilization of cocaine-cue memories

Authors: *B. CHO[1], H. SANCHEZ[1], R. J. DILEONE[1,2], J. TAYLOR[1,2,3];
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Abstract: Exposure to drug-associated cues (conditioned stimuli; CS) can trigger craving and relapse even after long periods of abstinence. One potential approach to reduce drug-seeking/taking behavior is to disrupt drug-cue associated memories by interfering with memory reconsolidation processes. Previous studies have shown that drug-associated cue memory reactivation (i.e., destabilization) followed by an amnestic agent can reduce drug-seeking in response to the reactivated cue. Key evidence suggests that memory destabilization requires the induction of a prediction error (PE) - a discrepancy between the expected and actual outcome. To investigate the impact of PE on drug-seeking behavior, we generated a negative PE by altering the magnitude (i.e., dose) of the drug (unconditioned stimulus) during memory reactivation. In Experiments 1, rats were trained to self-administer cocaine (0.5 mg/kg) paired with two separate cues - CS1 or CS2 - for a minimum of 12 days, followed by 8 days of extinction. For memory reactivation, rats were randomly divided into two groups. One group experienced a single presentation of CS1 with an unexpected magnitude of cocaine (0.1 mg/kg) to induce a negative PE, while the other group received a single CS1 presentation with the expected dose of cocaine (0.5 mg/kg) to induce no PE. Immediately afterward, the rats were systemically injected either with anisomycin (a protein synthesis inhibitor) or vehicle. The following day, cue-induced reinstatement was used as a test of cocaine-seeking for CS1 and CS2. Rats that received anisomycin following the negative PE during reactivation showed a significant reduction in cue-induced reinstatement for both CS1 and CS2, indicating that a negative PE initiates memory destabilization, rendering it susceptible to amnestic agents and reducing relapse-like behavior. In Experiment 2, we investigated the neural circuits involved. Rats were infused with AAV-DIO-hM4Di into the ventral tegmental area (VTA) and Cre recombinase into the nucleus accumbens (NAc), and later subjected to the same cocaine self-administration and extinction paradigm. Subsequently, they received an injection of either clozapine-N-oxide (CNO) or vehicle immediately after memory reactivation to block neural activity in VTA to NAc circuits. Notably, rats that received CNO after a negative PE during reactivation showed a significant decrease in cue-induced reinstatement for both CS1 and CS2 compared to the rats that received the vehicle. Our results indicate that projections from VTA to NAc are involved in memory reconsolidation processes that are triggered by the induction of a negative PE.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.13/NN5

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA048280

Title: Aversive white noise reduces nucleus accumbens core dopamine signaling and promotes both cocaine intake and escape behavior

Authors: *E. M. GRAFELMAN[1], D. S. WHEELER[1], L. M. VLACH[1], B. COTE[1], E. J. GEISE[1], G. N. PADULA[1], M. C. HEARING[1], J. R. MANTSCH[2], R. A. WHEELER[1]; [1]Biomed. Sci., Marquette Univ., Milwaukee, WI; [2]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Adverse life events are a primary cause of relapse to drug use in humans, and acute stressors can trigger drug seeking in rodents. In previous studies we observed that aversive stimuli can enhance ongoing cocaine self-administration. We have recently seen that intense (90dB), but not mild (55dB), white noise increases lever pressing for cocaine. This intense white noise also reduces dopamine in the nucleus accumbens (NAc) core and we hypothesize that the aversion-induced reduction in dopamine promotes cocaine seeking. To investigate whether that aversion signal is broadly associated with other aversively motivated behaviors, we tested the relationship between aversive white noise, negatively reinforced behavior, and NAc dopamine. Female and male Sprague Dawley rats (n=13 females, n=13 males) underwent surgery in which they received an infusion of AAV5-hSyn-dLight into the NAc core and implantation of an optic fiber to the same location. Following recovery, rats were trained in daily sessions to press levers for the delivery of a sucrose pellet. After stable responding was achieved on both levers at variable interval schedule (ranging from 30 to 150 seconds), rats were transitioned to negative reinforcement. In this phase, a white noise (either intense (90dB) or mild (55dB)) was intermittently presented and responses on one lever (active lever, counterbalanced) terminated the white noise while responses on the inactive lever had no consequence. If no response was made, the white noise timed out after 60s. The next trial started 6s after a timeout, or 11s after an active lever response. Intense white noise (but not mild white noise) significantly reduced dopamine signaling on the first day of negative reinforcement training ($F(1,20) = 9.21$, $p=0.007$). Consistent with this, animals exposed to intense white noise maintained responding on the lever that terminated the noise while rats exposed to mild white noise did not ($F(8,192) = 5.00$, $p < 0.0001$). Interestingly, following several days of training both mild and intense WN reduced dopamine significantly at onset ($F(1,18)=39.09$, $p<0.00001$), and ongoing studies are investigating this transition. Additionally, ongoing experiments are testing the influence of chronic stress on dopamine signaling. Specifically, we are testing the effect of chronic variable stress on dopamine release in response to intense white noise and measuring its effect on negatively reinforced behavior.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.14/NN6

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 2P20GM103432
NIH Grant DA046522

Title: Transient plasticity of neuronal ensembles for cocaine-seeking using self-administration and relapse model

Authors: *L. FLOM[1,2], S. HODGINS[1,3], A.-C. BOBADILLA[1,2];
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Abstract: One of the leading areas of research in neuroscience currently is neuronal ensembles, also known as subpopulations of co-activated neurons, that drive behavior. The present study is interested in examining the cocaine-seeking ensemble in the nucleus accumbens core, a significant integration center of the reward pathway. Previous literature has examined a concept known as transient plasticity or temporary changes to dendritic spines density and head diameter (d_h) in the nucleus accumbens core. That work has looked at the general population but examining the specific changes in the cocaine-seeking ensemble has yet to be completed. We hypothesized that d_h would be greater in actively seeking cocaine medium-spiny-neurons (MSNs). To accomplish this task, 8-10-week-old cFos-TRAP2 mice allow for endogenous tagging of the actively seeking MSNs with fluorescent marker tdTomato to analyze spine morphology. A model often used in substance use disorder (SUD) research is self-administration and relapse, a contingent model that allows delivering the drug based on the subject's willingness to take the drug. Acquisition of the self-administration includes two nose poke holes inside of an operant box, one hole that has an availability light as a cue and administers the drug (active), and one that is inert (inactive). Upon inserting its nose into the active nose poke, mice receive an infusion of cocaine (.5 mg/kg/infusion). The mice underwent ten days of extinction training, where the active nose poke no longer had the availability cue nor delivered cocaine, thus decreasing the interaction of the mice with the nose pokes. After extinction training, mice completed a 30-minute cue-induced reinstatement (RST1) showing the cue but not receiving cocaine, followed by an injection of Tamoxifen to allow expression of tdTomato within the seeking ensemble. To examine actively seeking vs. non-actively seeking spine morphology, an additional four days of extinction occurred, half of the mice received a second reinstatement (RST2), and half were sacrificed without RST2. Mice showed significant reinstatements. Comparing the groups showed no significant difference in d_h or spine density. A further study will be conducted to reduce the RST time to 15 minutes to see if the transient plasticity is shorter than 30 minutes.

Disclosures: **L. Flom:** None. **S. Hodgins:** None. **A. Bobadilla:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.15/NN7

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA046457

Title: Establishing the optimal dose for outcome devaluation via cocaine satiety

Authors: ***S. N. HANDEL**, R. J. SMITH;
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Abstract: Our lab recently developed a novel procedure to assess habitual responding for intravenous (IV) cocaine by using outcome devaluation via satiety. This method temporarily devalues cocaine by satiating the rat with experimenter-administered (i.e., noncontingent) cocaine infusions (Jones et al., 2022). We found sensitivity to outcome devaluation with cocaine doses that led to estimated brain concentrations similar to self-administered levels. However, lower doses did not result in satiety and much higher doses resulted in cessation of responding even in habitual rats. Thus, the purpose of this investigation was to further explore the concept of cocaine satiety and refine the cocaine devaluation procedure. We hypothesized that the optimal dose for cocaine satiety is based on mimicking an individual rat's brain cocaine concentrations achieved during self-administration. During self-administration, cocaine levels in the brain rise and fall according to the timing of infusions, creating peaks (high points) and troughs (low points) in a wave-like pattern. Previous data showed that individual rats are consistent in their average peak brain concentrations across sessions and that this correlates with the noncontingent cocaine dose needed to drive outcome devaluation (Jones et al., 2022). To further explore cocaine dosing, male Sprague Dawley rats were trained to self-administer IV cocaine on a seeking-taking chained schedule of reinforcement. For outcome devaluation, multiple doses of noncontingent cocaine were used on different sessions in a within-subject manner, and then responding was assessed in a 10-minute extinction test. For individual rats, we compared the estimated brain concentrations during the devaluation session to estimated brain concentrations achieved during self-administration (average peak and trough). We found that both goal-directed rats (n=11) and habitual rats (n=14) showed low levels of responding when brain concentrations were above their self-administration peak, and both showed higher levels of responding when brain concentrations were below their trough. However, only habitual rats responded when brain concentrations were between peak and trough, suggesting that this is the optimal dose for distinguishing habitual and goal-directed cocaine seeking. These results indicate that cocaine satiety via noncontingent cocaine is related to matching the cocaine brain concentrations experienced by individual rats during self-administration. At these cocaine levels, habitual rats are insensitive to outcome devaluation, whereas goal-directed rats are sensitive.

Disclosures: **S.N. Handel:** None. **R.J. Smith:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.16/NN8

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: R21NS114723
OIA-1632891

Title: Subsecond recordings of GABA and glutamate levels over 16 weeks in rat brain with microwire biosensors

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Abstract: Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter (NT) and glutamate (GLU) is the chief excitatory NT. Their balance, which can fluctuate on a subsecond time scale, is often impaired in disorders such as epilepsy and traumatic brain injury. Microdialysis can reveal NT levels, but not in real time with subsecond resolution. Enzymatic biosensors can detect NTs in real time for up to several days by producing an electroactive product, such as H_2O_2. However, GABA detection requires exogenous addition of substrate molecules which is not practical for recording in freely moving animals. We created a novel, real-time microbiosensor cartridge composed of microwires (MW) to detect GABA that uses α-ketoglutarate, a reaction product of glucose oxidase, as the substrate for GABASE which facilitates detection of GABA without added reagents. A second MW detected GLU and a third MW was coated without enzymes to detect and subtract current from interferent molecules. Our biosensor cartridge was inserted into a permanently implanted cannula in rat CA1 for recording GLU and GABA levels with subsecond time resolution in freely moving rats. A freshly calibrated biosensor cartridge was inserted into the cannula for biweekly recordings for up to 16 weeks. The geometry of the MW biosensor was more suitable than shank-style sensors for use in cell culture, brain slices, and in laminar regions of the brain in awake behaving rats. Tests in rat hippocampal brain slices show reproducible peaks. Recordings during sleep cycles in live rats show an increase in GABA baseline at sleep onset and a sharp decrease prior to waking. A recording during an epileptic seizure revealed interictal-like activity prior to the seizure and a prominent reduction in baseline GABA at seizure onset with a gradual increase at the end of the seizure. These results demonstrate the utility of this low-cost, high performance probe for longitudinal studies in rat models of disease.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: KBRI basic research program 23-BR-03-03
NRF-2021R1A2C2094627

Title: The emerging role of re-myelination on cocaine seeking behaviors in mice

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Abstract: Numerous studies have demonstrated various changes caused by chronic cocaine exposure in mice. While demyelination is known to be one of the consequences of cocaine use, the impact of cocaine on oligodendrocytes has yet to be determined. In the present study, we investigated neurobiological dynamics induced by chronic cocaine exposure, specifically focusing on 1) structural changes, 2) oligodendrocyte dysfunction, and 3) methods and effects of recovery. Initially, we observed that mice injected with cocaine for 5 days showed sensitization to cocaine after a 3-week withdrawal period. These mice demonstrated significant alterations in the thickness of myelin sheath and the expression levels of various oligodendrocyte-related genes, which are related to the oligodendrocyte maturation stage. To restore the myelin sheath, which is reduced by chronic cocaine exposure, we employed miconazole drug injection or viral injection of myelin basic protein (MBP) overexpression. Consequently, remyelination was able to restore mRNA levels of oligodendrocyte-related genes and inhibit cocaine-seeking behaviors. Collectively, our findings suggest that cocaine exposure induces functional impairment of oligodendrocytes, which could affect neuronal transmission. These results can provide a foundation for understanding the causal relationship between oligodendrocytes and neurons affected by cocaine, highlighting a potential target for ameliorating cocaine-induced deficits.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.18/NN10

Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA052169 to JRM
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E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals

Title: Exanination of cocaine vs. sucrose choice in rats using a within-session effort-based voliyional choice procedure

Authors: *M. ESTES[1], D. B. NOWAK[2], B. E. SCHULTZ[2], B. E. SCHULTZ[2], J. R. MANTSCH[2];
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Abstract: Rodent models used to investigate substance misuse have been limited by the assessment of drug self-administration (SA) using approaches that do not permit choice between the drug and alternative rewards. Recent efforts examining drug SA under a variety of choice conditions have revealed that rats will reliably choose non-drug reinforcers (e.g., sucrose, social interaction) over drugs when provided at comparable effort cost. While the economics of drug choice have been interrogated, such approaches have often required the systematic manipulation of effort requirements and/or reinforcer value across multiple experimental sessions, thus limiting their utility for investigating the effects of acute manipulations on behavior. Building upon these prior approaches, we have designed a model that encourages within-session, tractable choice between sucrose and cocaine. This model leverages a progressive-ratio (PR) schedule for sucrose while maintaining a fixed-ratio (FR) requirement for cocaine on a discrete trial basis. As rats generally prefer sucrose to drug at low cost, we observe a daily "switch point" in most subjects as they transition from sucrose to cocaine choice. In our exploratory studies, male and female adult Sprague Dawley rats were first trained to self-administer sucrose pellets in an operant chamber under a PR schedule. Following implantation of an intravenous catheter, rats were then trained to self-administer cocaine at either a high (0.8mg/kg/inf) or low dose (0.5mg/kg/inf) on a separate lever. After 7 days of stable SA (2hr/day), rats underwent their first of 12 choice sessions comprised of a 21 discrete trial format. Each trial allowed for a 7-min response period and a 2-min timeout following time expiration or reward delivery. The PR requirement for sucrose increased after each trial, while cocaine remained available at a low FR in all trials. Rats exhibited individual differences in daily switch points and drug vs. food choice ratio, termed drug choice index (DCI). Preliminary data demonstrate that the removal of cocaine or sucrose reinforcement promotes self-administration of the alternative reinforcer indicated by reduced switch points and higher DCIs when sucrose is eliminated and increased switch points and lower DCIs when cocaine is replaced by saline. Consistent with reports of sex differences in cocaine seeking, initial findings suggest that although female rats exert more effort when sucrose is the only reward option, they tend to switch to cocaine sooner and have a higher DCI than male

rats. Studies investigating the influence of drug dose and estrous cycle phase and the effects of acute food restriction or satiety are ongoing.

Disclosures: M. Estes: None. **D.B. Nowak:** None. **B.E. Schultz:** None. **B.E. Schultz:** None. **J.R. Mantsch:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: T32DA007027
P30DA033934
R36DA057546

Title: Effects of Chemogenetic Modulation of the Mesocorticolimbic Dopamine Pathway on Cocaine Choice

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Abstract: Rationale: The mesocorticolimbic dopamine pathway has been implicated in reinforcement processes. Pharmacological manipulations (e.g., amphetamine treatment) of dopamine neurotransmission have been shown to modulate cocaine-maintained behavior; however, many of these manipulations are not selective for the mesocorticolimbic pathway. The goal of the present studies was to determine effects of selective acute and chronic activation of the mesocorticolimbic dopamine pathway on cocaine-vs-food choice in male and female rats using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and the DREADD agonist deschloroclozapine (DCZ). A cocaine-vs-food choice procedure was utilized to dissociate DCZ effects on reinforcement processes (i.e, percent cocaine choice) vs. general behavioral effects (i.e. rates of operant responding). **Objective:** Use chemogenetics to investigate the effects of selective acute and chronic activation of the mesocorticolimbic dopamine pathway on drug-maintained behavior.**Methods:** Two experiments were conducted using adult male and female Tyrosine Hydroxylase (TH):Cre Sprague Dawley rats. Subjects were aseptically implanted with single-lumen catheters and responded under a concurrent “choice” schedule of food (32% liquid food) and cocaine (0-1.0 mg/kg/injection) during daily 2-h sessions. In the first experiment, animals (n=4) received acute DCZ pretreatment (vehicle, 1.0-1000 μg/kg) to determine the effect of acute activation of the mesocorticolimbic pathway on cocaine-vs-food choice. In the second experiment, the effect of chronic activation of the mesocorticolimbic dopamine pathway on cocaine-vs-food choice prior to and after bilateral intra-VTA hM3Dq DREADD expression was determined in rats (n=10) using continuous DCZ treatment (vehicle, 1.0-100 μg/kg/h). **Results:** Under baseline conditions, cocaine maintained a dose-dependent

increase in cocaine-vs-food choice. Chronic and acute DCZ administration prior to DREADD expression did not significantly alter cocaine choice. Acute pretreatment with 100 and 1000 µg/kg DCZ after DREADD expression increased cocaine choice. Continuous administration of DCZ after DREADD expression did not significantly affect cocaine-maintained behavior. **Conclusions:** Acute and chronic administration of DCZ prior to intra-VTA DREADD expression had no significant effect on cocaine choice behavior suggesting a degree of behavioral selectivity. The lack of effect during chronic DCZ treatment on cocaine choice post-DREADD expression suggests potential tolerance to DCZ treatment effects. **Supported by:** T32DA007027, P30DA033934, R36DA057546

Disclosures: H. Robinson: None. **M. Banks:** A. Employment/Salary (full or part-time):; Virginia Commonwealth University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institutes of Health.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.20/NN13

Topic: G.09. Drugs of Abuse and Addiction

Title: The effect of antibiotic and short chain fatty acid replacement on the reinstatement of cocaine-seeking behavior in female and male rats

Authors: M. VERHOEVEN[1,2], J. WASHINGTON[1,2], ***T. S. DENNIS**[3,2];
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Abstract: The misuse of drugs continues to be a major public health concern. Gaining a better understanding of factors that contribute to addiction is crucial in developing effective treatments to reduce its impact on the individual and society. One promising line of research has focused on how gut microbiota influence reward processing and relapse. For example, inducing gut dysbiosis through the chronic administration of antibiotics increases the rewarding properties of cocaine through conditioned place preference and increases reinstatement of drug seeking for cocaine in a self-administration paradigm. Interestingly, supplementing the antibiotic treatment with short chain fatty acids (SCFAs), the brain-active metabolites of gut bacteria, reduces both the rewarding properties of cocaine and drug-seeking in a cue-induced reinstatement test. However, the bulk of these studies focus exclusively on a male population. Our work seeks to understand whether the effects of gut dysbiosis and SCFA replacement in male rats also extends to female rats. In the current project, adult female and male sprague dawley rats were trained to self-administer cocaine (0.75mg/kg/infusion) for 14 days (criterion of 10 infusions/session) in two-hour sessions. After the last day of self-administration, rats underwent forced home cage

abstinence for four weeks. On the first day of abstinence, one group of rats had a cocktail of antibiotics (Bacitracin 0.5mg/ml, Neomycin 2mg/ml, Vancomycin 0.2mg/ml and Pimaricin 1.2μg/ml) added to their drinking water, while the rest remained on standard water. Two weeks later, half of the rats in the antibiotic group had SCFAs (67.5mM acetate, 40mM butyrate, 25.9mM propionate) also added to their water. These treatments continued throughout the remainder of the experiment. Following abstinence, all rats underwent 1) an initial round of extinction with a criterion of less than 10 active lever presses on average over three consecutive days, 2) cue-induced reinstatement procedures, in which an active lever press resulted in the presentation of a 5 second light-tone cue previously associated with cocaine administration, 3) a second round of extinction with the same criterion as the first, and 4) a stress-induced reinstatement test, in which rats receive intermittent foot shocks for 10 minutes prior to testing. Preliminary results suggest that in male, but not female rats, adding SCFAs to the drinking water marginally reduces cue-induced reinstatement when compared to the antibiotic-treated male rats. Our current sample size is 5-8 rats per group, so more work is currently underway to confirm these findings.

Disclosures: **M. Verhoeven:** None. **J. Washington:** None. **T.S. Dennis:** None.

Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.21/NN14

Topic: G.09. Drugs of Abuse and Addiction

Title: Bile acids modulate reinstatement of cocaine conditioned place preference and accumbal dopamine dynamics without compromising appetitive learning

Authors: *D. ZANELLA[1], N. K. SMITH[3], A. J. HARDAWAY[2], A. BUCHANAN[1], C. H. MULLINS[1], A. GALLI[1], A. M. CARTER[1];
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Abstract: Psychostimulants target the dopamine transporter (DAT) to elicit their psychomotor actions. Bile acids (BAs) can also bind to DAT and have been shown to reduce behavioral responses to cocaine, suggesting a potential therapeutic application of BAs in psychostimulant use disorder. Here, we investigate the potential of BAs to decrease drug-primed reinstatement when administered during an abstinence phase. To do this, after successful development of cocaine-associated contextual place preference (cocaine CPP), cocaine administration was terminated, and animals initiated on treatment with vehicle or obeticholic acid (OCA). When preference for the cocaine-associated context was extinguished, mice were challenged with a single priming dose of cocaine, and reinstatement of cocaine-associated contextual preference was measured. Animals treated with OCA demonstrate a significantly lower reinstatement for cocaine CPP. Using electrically evoked amperometry on brain slices containing nucleus

accumbens, we also show that OCA impairs the ability of cocaine to reduce the clearance rate of the amperometric signal and diminishes its area under the curve (AUC). Furthermore, the AUC of the amperometric signal positively correlates with the reinstatement index. Finally, using operant feeding devices, we demonstrate that OCA has no effect on contextual learning or motivation for natural rewards. These data highlight OCA as a potential therapeutic for cocaine use disorder.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant RO1DA047785
NIH Grant T32DA043469

Title: Exploring the role of cholinergic drive to α7 expressing GLP-1 neurons in cocaine reward

Authors: L. RIEDY[1], ***A. SALAZAR**[1], C. MAKHLOUTA LUGO[1], Q. KONG[2], M. XU[2]; [1]Univ. of Chicago, Chicago, IL; [2]Dept. of Anesthesia and Critical Care, The Univ. of Chicago, Chicago, IL

Abstract: Glucagon-like peptide-1 (GLP-1) is a key regulator of insulin homeostasis and satiety. As such, GLP-1 receptor (GLP-1R) agonists are widely used to treat type 2 diabetes and obesity. GLP-1R agonists are emerging as a potential new therapeutic for cocaine and other substance use disorders as they have been shown to attenuate drug seeking behavior for a variety of drugs of abuse, including cocaine seeking and taking. Cholinergic signaling throughout the central nervous system has been strongly implicated in the development and persistence of addictive disorders, including cocaine misuse. The primary source of centrally acting GLP-1 is neurons in the caudal portion of the NTS (cNTS). Putative cholinergic terminals and acetylcholinesterase (AChE) expression in the NTS and evidence of α5-containing nicotinic acetylcholine receptors (α5* nAChRs) expressed on GLP-1 neurons suggests cholinergic drive may play a role in modulating endogenous GLP-1 activity; however, it remains unclear if endogenous cholinergic signaling acts on these neurons to regulate drug seeking behavior and if so, what the source of those cholinergic inputs may be. In the present project, we have collected cNTS slices from 3 c57BL/6 male mice and comprehensively tested mRNA expression of nicotinic (*Chrna*5,7, *Chrnb*2-4) and muscarinic (*Chrm1-5*) cholinergic receptors on neurons that express GLP-1 (*Gcg*) using RNAScope based fluorescence *in-situ* hybridization (FISH). We have found that separate groups of GLP-1 neurons in the cNTS express the α5* and α7* nAChR subunit. Furthermore, local infusion of an α7 nAChR agonist, PHA-543616 into the cNTS significantly attenuates the

acquisition of cocaine conditioned place preference (CPP) (p=0.0300). These results suggest a role for cholinergic drive to α7 expressing GLP-1 neurons in the attenuation of cocaine reward. Finally, we expressed a pan neuronal genetically encoded calcium sensor, GCaMP8s, and implanted a fiber optic cannula into the cNTS of a male c57B/L/6 mouse and performed the first known fiber photometry recording of the cNTS. By investigating these cholinergic circuit-receptor interactions, we hope to elucidate the role of acetylcholine signaling in GLP-1 mediated regulation of addictive behaviors.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA 1R01DA055008

Title: Vagus nerve stimulation (VNS) alters activity in networks that regulate drug-seeking

Authors: *C. DRISKILL, S. JALIVAND, F. SALAZAR, N. SUJI, A. KHAN, J. T. O'BRIEN, L. VU, S. TATA, R. NUNA, Z. KANWAL, N. MOLIN, S. KROENER;
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Abstract: Substance use disorder is a chronic relapsing condition often marked by the inability to cease drug use despite negative outcomes. Environmental stimuli presented during drug taking become hyper-salient reward indicators or cues and can make abstaining from drugs difficult. Extinction is a learning process that can reduce the power of these cues by creating a neutral association with a previously drug paired cue. Unfortunately, extinction-based therapies have had limited success in long term prevention of relapse. Our lab has previously shown that vagus nerve stimulation during extinction training from drug-seeking behavior reduces drug seeking during cue-induced reinstatement. Additionally, we found changes between rats given VNS versus Sham stimulation in the expression of immediate early genes in regions associated with reinstatement. The medial pre-frontal cortex (mPFC) is implicated in the regulation of drug seeking behavior, but little is known about the networks that drive mPFC activity during cue-induced reinstatement. Here we tested how pairing extinction learning with VNS alters expression of the immediate early gene cFos during reinstatement in networks that converge on the mPFC.We infused a GFP expressing retrograde AAV into either the infralimbic cortex (IL) or prelimbic cortex (PL) to label cells that project to the mPFC. Rats self-administered cocaine for 15 days and then underwent 10 days of extinction training with VNS or sham stimulation, followed by cue-induced reinstatement. Rats were sacrificed after reinstatement and tissue from regions associated with reinstatement were stained for cFos as a marker of neuronal activity. We

then quantified how VNS altered the total number of cFos-positive cells, as well as the co-localization of cFos+ cells that project to the mPFC. In the BLA we found VNS decreased co-localizations in the IL-projecting neurons, but not in the PL-projections. In the PVT VNS lead to an increase in co-localizations for both IL and PL projecting neurons. We hypothesize that these changes in neuronal activity in mPFC-projecting neurons contribute to the VNS-induced suppression of drug seeking during cued reinstatement. These results help us gain a better understanding of the mechanisms of how VNS facilitates extinction learning from drug seeking behavior.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R25GM113262
NIH Grant R01DA038613

Title: Cell type selective alterations to medium spiny neuron dendritic complexity in the striatum following high fat exposure

Authors: *I. A. WILLIAMSON[1], C. A. CALARCO[2], C. BARRETT[3], M. LOBO[4];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Parkville, MD; [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Univ. Of Maryland Baltimore, Baltimore, MD; [4]Univ. Of Maryland Sch. of Med., Baltimore, MD

Abstract: The effects of a diet high in fat on reward processing is a growing area of interest. Despite this, the neuronal mechanisms mediating these alterations have yet to be discovered. The striatum, including the Nucleus Accumbens (NAc), dorsal medial striatum (DMS), and dorsal lateral striatum (DLS), is of particular interest due to its roles in associative learning with rewards, motor function, and habit formation. In particular, dopaminergic and glutamatergic signaling changes have been observed following a high fat diet (HFD) in the DMS and DLS. To understand morphological changes downstream of this altered signaling, we looked at multiple measures of dendritic complexity in male and female mice that consumed HFD. We examined these changes in a cell-type selective manner, identifying D1 and D2 MSNs, neurons that express D1-like and D2-like receptors, respectively. After stereotaxic injection of low titer DIO-eYFP virus in each brain region of interest, D1-Cre or A2A-Cre Mice were exposed to HFD (45% fat) or standard lab chow (12% fat) for either one week or one month. Identified D1 and D2 medium spiny neurons in the NAc, DMS, and DLS were imaged at 40x on a confocal microscope and

analyzed using Imaris software. We used three measurements of dendritic morphology, branch points, dendrite length, and sholl intersections, revealing brain region-specific and cell type-specific changes following HFD. In the one-week time point, we observed a trending increase in branch points in NAc D1 MSNs, but a decrease in D2 MSNs. In the dorsal striatum, DLS D2 MSNs showed reduced dendrite length and sholl intersections, while we observed no changes in D1 MSNs or changes in either cell type in the DMS. At the one-month time, dendritic complexity changes appeared in the DMS, with D1 MSNs having increased dendrite length and sholl intersections, with no changes in D2 MSNs or DLS. In NAc, when looking at D2 MSNs, there was a decrease in dendrite length and sholl intersections. Together, these changes could suggest changes in synaptic plasticity and changes in neuronal communication that develop over long-term HFD exposure. These findings are specific to male mice, and analysis of female data is ongoing. Future work should examine dendritic spine density and morphology of MSNs to further understand signaling changes after HFD. Furthermore, these changes in dendritic morphology are likely the result of changes in molecular and cellular processes. To further investigate this, synapse- and morphology-related gene expression changes should be observed at the same two time points. Ultimately, this will aid in understanding how a HFD leads to alterations in reward processing throughout the striatum.

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Poster

PSTR104. Cocaine Self-Administration, Circuits, and Drug-Seeking

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR104.25/NN18

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CONACYT Grant 284771

Title: Dopamine D2R antagonist improves glucose homeostasis targeting different white adipose tissues in diet-induced obese female and male mice

Authors: *D. VÁZQUEZ CARRILLO[1], A. L. OCAMPO-RUIZ[1], A. BAEZ-MEZA[1], G. RAMIREZ-HERNANDEZ[2,3], E. ADAN-CASTRO[1], J. GARCIA-RODRIGO[1], J. DENA-BELTRAN[1], E. DE LOS RÍOS-ARELLANO[1], M. SANCHEZ-MARTINEZ[1], G. ORTIZ-ARBALLO[1], G. MARTINEZ DE LA ESCALERA[1], C. CLAPP[1], Y. MACOTELA[1];
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Abstract: Reduced PRL levels correlate with higher risk/prevalence of metabolic diseases. In obese male rats with low PRL levels, treatment with PRL improves metabolic parameters. Therefore, our hypothesis is that drugs that increase PRL, such as sulpiride, an antagonist of dopamine D2 receptor, could have beneficial effects against obesity-derived metabolic alterations. To see if we could imitate the beneficial effects of increasing PRL in obese rats, we

aimed to evaluate whether sulpiride would improve obesity-derived metabolic alterations in obese male and female mice, by increasing PRL levels. For this, C57BL/6 8-week-old mice fed a high-fat diet for 8 weeks to induce obesity, were administered daily with 30 mg/kg of sulpiride during the last 4 weeks of the diet. To test whether sulpiride effects were mediated by PRL action, we used the same protocol in mice null for the PRL receptor (*Prlr*-KO*)*. Sulpiride induced a larger increase in PRL levels in females than in male mice: around 70 ng/mL in control and obese male mice, and 113 ng/mL in control and 147 ng/mL in obese female mice. In obese males sulpiride decreased hyperglycemia, insulin resistance and triglyceride levels, without affecting body weight or caloric intake; and in females, sulpiride treatment decreased hyperglycemia, without alterations in insulin, triglyceride levels, body weight or caloric intake. Interestingly, sulpiride also decreased hyperglycemia in obese males null for the Prlr. Sulpiride reduced hypertrophy in visceral adipose tissue of obese males and normalized the expression of hypoxia inducible factor 1a (a marker of hypoxia), and of the *Prlr*, the insulin receptor and the glucose transporter 4 (markers of insulin sensitivity), all altered in obesity. Meanwhile, in obese females, sulpiride increased subcutaneous adipose tissue weight and the number of adipocytes. In conclusion, in both obese male and female mice, sulpiride reduces hyperglycemia and improves metabolic parameters, and at least in males its effects are independent of PRL actions.

Disclosures: **D. Vázquez Carrillo:** None. **A.L. Ocampo-Ruiz:** None. **A. Baez-Meza:** None. **G. Ramirez-Hernandez:** None. **E. Adan-Castro:** None. **J. Garcia-Rodrigo:** None. **J. Dena-Beltran:** None. **E. de los Ríos-Arellano:** None. **M. Sanchez-Martinez:** None. **G. Ortiz-Arballo:** None. **G. Martinez de la Escalera:** None. **C. Clapp:** None. **Y. Macotela:** None.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.01/NN19

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant MH121454
NIH Grant GM133421

Title: Psilocybin analog 4-OH-DiPT enhances fear extinction and GABAergic inhibition of principal neurons in the basolateral amygdala

Authors: *T. KELLY[1], E. M. BONNIWELL[2], L. MU[1], X. LIU[1], V. FRIEDMAN[1], H. YU[3], J. MCCORVY[2], Q.-S. LIU[1];
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Abstract: Psychedelics possess therapeutic potential for numerous mood and trauma-related mental health disorders. Unfortunately, most clinically studied psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, have a long duration of action that poses practical

limitations for clinical use. Most psychedelics exert their psychoactive effects at the serotonin 5-HT_{2A} receptor, where agonists have been shown to enhance fear extinction via the basolateral amygdala (BLA). First, we set out to characterize the pharmacological profile of 4-OH-DiPT, a purported shorter duration derivative of psilocybin, using a 5-HT GPCRome BRET platform, which is capable of interrogating all 12 human serotonin G protein-coupled receptors (GPCRs) measuring G protein dissociation. We show that 4-OH-DiPT shows strongest agonist activity at all three 5-$HT_{2A/2B/2C}$ receptors with near full agonist activity at 5-HT_{2A} (93% of 5-HT). When administered to mice in a fear extinction paradigm, 4-OH-DiPT significantly reduces freezing responses to conditioned cues and enhances extinction memory the following day. The 4-OH-DiPT-treated mice showed reduced avoidance behavior in novelty-suppressed feeding, which was associated with a decrease in the excitation to inhibition (E/I) ratio in the BLA. 4-OH-DiPT produced robust increases in spontaneous inhibitory postsynaptic currents (sIPSCs) in BLA principal neurons and action potential firing in BLA interneurons. RNAscope demonstrates that *Htr2a* mRNA is expressed predominantly in BLA GABA interneurons. Our findings suggest that 4-OH-DiPT activates BLA interneurons via the 5-HT_{2A} receptor, which results in enhanced GABAergic inhibitory input to BLA principal neurons, the resultant augmentation of GABAergic inhibition provides a potential mechanism for enhanced extinction of fear cues.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.02/NN20

Topic: G.09. Drugs of Abuse and Addiction

Title: Neural complexity measures reflect aperiodic activity

Authors: *Q. VAN ENGEN[1], N. LU[2], B. VOYTEK[2];
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Abstract: Neural activity is characterized by its complex dynamics, which are often quantified using tools adapted from information theory such as signal entropy or Lempel-Ziv complexity (LZc). These measures have been correlated robustly with different states of consciousness, however their physiological underpinnings are not clear. Brain complexity as measured by, for example, the LZc algorithm is reduced after rats receive propofol, or when in NREM sleep, compared to awake. And it is increased after the administration of psychedelics (such as ketamine). In contrast to measures of signal complexity, aperiodic activity is measured from the neural power spectrum and is mathematically linked to the autocorrelation of the neural signal. This arrhythmic brain activity is argued to reflect the total contribution of postsynaptic currents, partially capturing neural excitation/inhibition (E:I) balance in multiple recording modalities (LFP, EEG, and iEEG). This physiological grounding makes aperiodic activity more biologically

interpretable. Similar to complexity measures, aperiodic activity, as measured from the spectral exponent, is steeper when people are under propofol anesthesia that increases GABA in the brain, but flatter when ketamine is administered.Here, using ketamine as a use case, we test the hypothesis that LZc and aperiodic activity are largely capturing the same process. We hypothesize that increases in LZc complexity should be reflected as flatter aperiodic activity. Therefore, LZc and aperiodic exponent move in opposite directions from awake to sleep and anesthetics. Which means they might be inversely capturing the same physiological mechanism. In fact, this is shown in simulation work where E:I balance non-linearly affects aperiodic exponent and LZc.However, this relationship has not been replicated in human data yet. We have re-analyzed a dataset where participants received a sub-anesthetic dose of ketamine (Farnes et al., 2020). The original paper finds an increase in LZc in the ketamine condition from normal awake. First, we replicate the original findings using Linear Mixed Models (LMM), that brain state significantly predicts LZc. Second, using spectral parameterization, we find a significant decrease in aperiodic exponent from awake to ketamine. Another LMM shows that LZc can be predicted by the aperiodic exponent, over all conditions. Thus, showing a significant relationship between LZc and aperiodic exponent. These results support the notion that LZc and aperiodic exponent are capturing underlying E:I balance in the brain. And gives us an initial indirect hypothesis on the underlying physiology of brain complexity measurements.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.03/OO1

Topic: G.09. Drugs of Abuse and Addiction

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Title: Determining the role of dose and 5-HT_{2A}R activation in the lasting affective behavioral effects of psilocybin

Authors: *M. FARINHA-FERREIRA[1,2,3], C. GALIPEAU[1,2], J.-C. MARIANI[3], S. DIEBOLT[3,4,5], L. BARTHE[3,4,5], R. SANTOS[3], Z. LENKEI[3], A. M. SEBASTIÃO[1,2];
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Abstract: Interest in the 5-HT_{2A}R agonist psilocybin for the treatment of several neuropsychiatric disorders has recently increased, with human studies showing psilocybin to induce persistent mood improvements, and alterations in resting-state functional connectivity patterns. However, questions remain about the role of dose, and of 5-HT_{2A}R activation, in the emergence of such persisting actions, with pre-clinical work being necessary to fill these lacunae.

Here, we present two studies, using male 10-week-old C57BL6/J mice, aiming at determining the role of dose and 5-HT_{2A}R activation in persistent psilocybin affective behavioral effects. In study 1, mice (n = 12) received a single i.p. injection of either vehicle, 1, 5 or 10 mg/kg psilocybin. In study 2, mice (n = 18 - 20) received two i.p. injections spaced 30 minutes apart: the first containing either vehicle or the selective 5-HT_{2A}R antagonist MDL100907 (0.5 mg/kg), and the second containing either vehicle, psilocybin (5 mg/kg) or the non-hallucinogenic 5-HT_{2A}R agonist lisuride (0.8 mg/kg). In both studies, head-twitch response (HTR) quantification was performed immediately post-injection, with testing for affective behavior changes - consisting of the novelty-suppressed feeding (NSFT), open field (OFT), marble burying (MBT), sucrose (ST), and forced swim tests (FST) - beginning after 7-days.

In study 1, HTR frequency increased after psilocybin administration, plateauing at 5 mg/kg. 7-days after injection all psilocybin doses significantly decreased feeding latency in the NSFT, and both the 5 and 10 mg/kg doses significantly decreased buried marbles in the MBT. Conversely, OFT, ST and FST performances were unaffected by any treatment. Composite z-score measures reflected these effects, with 5 and 10, but not 1 mg/kg, inducing significant reductions in negative emotionality.

In study 2, both acute and persistent psilocybin effects replicated those observed in study 1, with additional increases being observed in total distance travelled in the OFT, and latency to immobility in the FST. Importantly, both the acute and long-term effects of psilocybin were blocked by MDL100907 pretreatment and were not replicated by lisuride treatment.

In conclusion, psilocybin induces significant, dose-dependent, reductions in negative emotionality, which are dependent upon 5-HT_{2A}R activation. Moreover, 5-HT_{2A}R activation, while necessary appears to not be sufficient for the emergence of psilocybin effects, as shown by the absence of lisuride effects. These results highlight 5-HT_{2A}R as the key player in psilocybin-induced behavioral effects, with future work focusing on their molecular and functional correlates.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.04/OO2

Topic: G.09. Drugs of Abuse and Addiction

Title: Stroboscopic stimulation as a model of the hallucinogenic brain: evidence from alpha power, E/I balance, and signal complexity modulation

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Abstract: It is hard to predict the moment when a hallucination will occur. Therefore, it is difficult to make precise, repeatable neural measurements during these experiences. To overcome this concern, researchers have started to employ experimentally induced models of hallucination (Rogers et al., 2021). One such model is stroboscopic (strobe) hallucinations (Purkinje, 1823). If a bright light is flickered at frequencies below 40Hz, a range of dynamic geometric visual hallucinations is experienced. Interestingly, strobe-induced hallucinations correlate with two EEG signatures of the hallucinogenic brain: alpha power reductions and signal complexity increase (Schwartzman et al., 2019), suggesting a correspondence between strobe hallucinations and the geometric patterns experienced during hallucinogen administration (Bartossek eta l., 2021; Amaya et al., 2023). However, these EEG signatures have only been tested at hallucinatory flicker frequencies. Therefore, it is unknown if they are correlates of geometric percepts specifically, or visual excitation due to flickering bright lights more generally. In this study, we examined the correspondence between these brain states in two ways. First, by comparing alpha power and signal complexity modulation during hallucinatory and non-hallucinatory stroboscopic stimulation. Second, by testing whether an EEG signature of increased excitation in the hallucinogenic brain, flattening of the 1/f slope (Muthukumaraswamy & Liley, 2018), is also observed during stroboscopic hallucinations. In a within-subjects design (n=13), EEG was recorded during hallucinatory (11Hz - 19Hz) and non-hallucinatory (51Hz - 59Hz) stroboscopic stimulation. As expected, stimulation with hallucinatory flicker-frequencies led to the perception of geometric patterns and this was associated with reduced alpha power, increased signal complexity, and a flatter 1/f slope, compared to baseline. However, a similar pattern of results was observed for non-hallucinatory flicker frequencies. From these results, we conclude that these three EEG measures are correlates of visual stimulation in general, not geometric hallucinations specifically. However, our results also demonstrate that both strobe stimulation and hallucinogens have remarkably similar effects on the brain, at least with respect to these measures: both produce a more excited and more complex brain state. This suggests that strobe stimulation is a viable model of hallucinogens. Future studies can use this model to develop analyses that dissociate between strobe with and without geometric percepts, which in turn can be tested during hallucinogen administration.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

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Topic: G.09. Drugs of Abuse and Addiction

Support: DFF 0169-00030B
DFF 5053-00036B

Title: Microdosing with psilocybin in rats increases resistance to stress, lowers compulsive actions, and strengthens cortical connections to the paraventricular thalamic nucleus.

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Abstract: Single psychedelic doses of psilocybin, the psilocin prodrug found in mushrooms of the genus *Psilocybe* ("magic mushrooms"), in combination with psychotherapy, show efficacy in treating depression, anxiety, and substance use disorders. Microdosing refers to the repeated use of psilocybin or mushrooms at non-hallucinogenic doses. While adherents of microdosing often report improved mental health, such reports are often anecdotal, highly biased, and especially vulnerable to placebo effects, especially in the context of retrospective studies. Nonetheless, microdosing is gaining traction for psychotherapeutic purposes as a non-hallucinogenic alternative to high doses of psilocybin.
Here, we established and validated a three-week psilocybin microdosing regimen in rats, based on the *in vivo* occupancy at rat brain 5-HT2A receptors using positron emission tomography (PET) with the selective 5-HT2A antagonist [18F]MHMZ. We correlated occupancy findings with the behavioral assessment of wet back shakes, a rat index of psychedelic action similar to the mouse head shakes, as well as other behavioral outcomes during and after the microdosing regimen, including sucrose preference, open field, elevated plus maze and pre-pulse inhibition of the startle response. At the end of the experiments, we assessed the levels of target receptors and synaptic vesicle glycoprotein 2A (SV2A), a surrogate marker of synaptic density.
The microdosing regimen resulted in below 20% occupancy at 5HT2A receptors in vivo, without increasing wet back shakes. Furthermore, microdosing did not cause anhedonia, anxiety, or deficits in pre-pulse inhibition of the startle response, nor did it downregulate or desensitize 5-HT2A receptors. However, in contrast to saline-injected controls, microdosing of psilocybin imparted resistance to stress-induced anhedonia from multiple subcutaneous injections, while also reducing the frequency of self-grooming (a proxy for compulsive actions), and increasing 5-HT7 receptor expression and synaptic density in the paraventricular nucleus of the thalamus. These results substantiate anecdotal reports of psilocybin microdosing effects as a therapeutic intervention pointing to a possible physiological mechanism.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.06/OO4

Topic: G.09. Drugs of Abuse and Addiction

Support: Tiny Blue Dot Foundation

Title: Cell-type specific cellular actions of psychedelic drugs, psilocybin and psilocin on mouse cortical neurons

Authors: ***M. KIM**[1], D.-W. KIM[1], S. VARGAS[1], L. NG[2], B. E. KALMBACH[2], S. OWEN[3], E. LEIN[2], J. T. TING[4], H. ZENG[1], C. KOCH[1];
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Abstract: Psilocybin and other serotonergic hallucinogenic drugs can profoundly alter consciousness and have recently come to the forefront regarding their therapeutic potential for treating a range of debilitating conditions. Although it is known that acute psychedelic effects lasting 1-2 hours depend on 5-HT2A receptor activation, psilocybin and its psychoactive metabolite psilocin also bind to and activate other serotonin receptor subtypes. In addition, relatively little is known about cell-type specific actions of these drugs in the brain. We performed Act-seq experiments (*in vivo* drug administration followed by single cell RNA-sequencing) to identify the distinct neuron types activated by psilocybin in the mouse brain. Specifically, Act-seq was used to detect acute psilocybin-induced changes in immediate early gene (IEG) expression as a surrogate for neuronal activation. Drug induced changes in IEG expression were determined by comparing psilocybin (1 mg/kg) versus saline condition at one hour post injection. A significant increase in IEG expression was found in layer 5 (L5)

intratelencephalic (IT) and near-projecting (NP) neurons in the medial prefrontal cortex (mPFC) and orbitofrontal cortex (ORB) regions. We also detected increased IEG expression in the vasoactive intestinal peptide (Vip) subclass of cortical GABAergic neurons. To directly probe drug induced changes in single cortical neuron properties we performed targeted Patch-seq experiments in mouse brain slices using focal application of psilocin. L5 IT, NP, and ET glutamatergic neuron types were targeted for recordings using transgenic or viral labeling strategies. We measured drug induced changes in membrane potential at rest, as well as changes in firing rate during sustained depolarizing current injection. In a subset of the experiments, we recovered cell morphology and transcriptomes and analyzed these data to corroborate cell type identity and to explore the correlation of drug effects with serotonin receptor gene expression. Psilocin-induced membrane depolarization (PID) was the predominant mechanism observed in L5 NP neurons, whereas psilocybin-induced hyperpolarization (PIH) was the predominant mechanism in L5 ET neurons. L5 IT neurons showed mixed PID or PIH responses. Our results suggest that neuromodulatory effects of psilocybin/psilocin in mouse mPFC L5 neurons act in a projection target-specific manner. Additional work is underway to obtain Patch-seq data from Vip neurons and additional types of L5 IT neurons in mPFC/ORB regions for comparison to the Act-seq data and to further explore the cell-type specific mechanism of action.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.07/OO5

Topic: G.09. Drugs of Abuse and Addiction

Title: Effects of psilocybin on metabolic activity and connectivity within the CSTC circuit in rats

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Abstract: Pharmacotherapy using psilocybin, a serotonergic psychedelic prodrug, demonstrates promising benefits in neuropsychiatric disorders like major depressive disorder and obsessive-compulsive disorder. While the psychedelic effects are short lived, therapeutic benefits persist long after psilocybin administration. The cortico-striato-thalamo-cortical (CSTC) circuit is hypothesized to play a role in mediating these effects, although the precise mechanism remains unclear.

Here we assess the acute and long term (one week post administration) effects on regional glucose metabolism and metabolic connectivity within the CSTC circuit after administration of a single dose of psilocybin in rats. Long-Evans rats (n=12) were fasted overnight prior to FDG PET recordings (baseline, acute, and one week post) for mapping of glucose metabolism and metabolic connectivity. All rats received saline or psilocybin (1 mg/kg) five min prior to FDG administration. Regional standardized uptake values (SUV) were normalized to the average whole brain FDG uptake. Time effects on FDG metabolism were analyzed using two-way ANOVA. Metabolic connectivity was analyzed as changes in pairwise Fisher's r-to-z transformed Pearson's correlation coefficients of normalized SUVs across subjects, between conditions (baseline, acute, one week). Significance in correlational changes were found through permutation testing. Furthermore, a control group (n=5) receiving saline at each scan was added. Following acute administration of psilocybin, we found a significant increase ($p<0.0001$) in FDG uptake in striatum, relative to baseline. FDG uptake in thalamus was unchanged after acute administration but significantly increased ($p=0.0101$) after one week. No changes were observed in the control group.

Metabolic connectivity analysis revealed significant changes in correlations between brain regions. Between baseline and acute conditions, there was a significant strengthening of the correlation between orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) ($p=0.0239$). Additionally, a negative association between OFC and the ventral tegmental area (VTA) was disrupted ($p=0.0128$). Between baseline and one week we found a significant increase in positive correlation between thalamus and mPFC ($p=0.0468$).

These findings demonstrate that a single dose of psilocybin can induce persistent changes in metabolic connectivity within the rat CSTC circuit. This aligns with clinical observations of prolonged therapeutic effects beyond the acute drug phase. Moreover, our analysis method can be extended to explore other drug-circuit interactions at the neural circuit level.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

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Program #/Poster #: PSTR105.08/OO6

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH P30DA033934

Title: The effect of the psychedelic psilocybin on nicotine dependence behaviors in preclinical models

Authors: *B. BUZZI[1,2], A. JASTER[2,3], N. MADAKASIRA[2], J. GONZÁLEZ-MAESO[3], M. I. DAMAJ[2];
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Abstract: Smoking remains a leading cause of preventable death and disease in the United States, with current pharmacotherapies having low efficacy. Thus, there is a need to explore new potential therapies. Psychedelics have been recently proposed as a potential therapeutic agent for numerous neuropsychiatric disorders, including substance use disorder; in particular, for smoking dependence. Our study uses a mouse model to study the effect of psilocybin, a classical psychedelic, on nicotine dependence behaviors. Male and female young adult mice were implanted subcutaneously with osmotic mini pumps containing nicotine, with a flow rate of 24 mg/kg/day for 14 days. 1 hour following mini-pump removal, mice were injected intraperitoneally (i.p.) with psilocybin (1 mg/kg) and assessed the following day for spontaneous nicotine withdrawal somatic signs. A separate cohort of serotonin (5-HT) 2A receptor knockout (KO) mice were tested in the same paradigm to determine the necessity of the 5-HT2A receptor, a receptor thought to be responsible for the "hallucinogenic" effects of psychedelics. Additionally, mice were tested for nicotine conditioned place preference (CPP) via 3 days of drug conditioning to a drug-paired side in a three-chamber box in the CPP test. Following the last nicotine conditioning day, mice were injected with psilocybin (1 mg/kg i.p.) and tested for nicotine preference in a drug free state the following day. Psilocybin completely reversed somatic signs due to nicotine withdrawal in mice. The effect of psilocybin was lost in the 5-HT2A KO mice, establishing this receptor as a potential mechanism of this attenuation. Additionally, psilocybin decreased the expression of nicotine preference in mice in the CPP paradigm. Psilocybin reduced the somatic signs of nicotine withdrawal and nicotine conditioned reward in mouse by action through the 5-HT2A receptor. These initial studies suggest that classical psychedelics like psilocybin may be a potential effective treatment for smoking cessation.

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Poster

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T32-MH020030 (JY)
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Title: Pharmacological characterization of quipazine analogs as a new structural class of psychedelic 5-HT_{2A} receptor agonists

Authors: *J. YOUNKIN[1,2], A. PAYMODE[3], A. M. JASTER[1,4], J. L. MALTMAN[1,5], J. ROLQUIN[1], G. D. MILLER[1], R. ABEDI[1], I. S. RAMSEY[1], R. A. GLENNON[3], M. DUKAT[3], J. GONZALEZ-MAESO[1];
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Abstract: Psychedelics are currently hot topics in molecular psychiatry and medicinal chemistry research. As more psychedelics are shown to produce desirable therapeutic effects in individuals with psychiatric conditions such as depression and substance use disorder, the clinical potential of these drugs becomes increasingly relevant, despite their negative reputation from the 1960s and 70s. It is accepted that psychedelics produce mind-altering effects such as hallucinations and expansion of consciousness acting mainly via the 5-HT_{2A} receptor (5-HT_{2A}R) - a G protein-coupled receptor involved in processes related to cognition, perception and mood. Structurally, classical psychedelics generally fall into two main categories: phenethylamines such as mescaline and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), and tryptamines which can be subdivided into simple tryptamines such as psilocybin and ergolines such as lysergic acid diethylamide (LSD). We recently reported that quipazine might represent a new group of psychedelics since it lacks a phenethylamine or tryptamine scaffold embedded in its structure. However, the clinical use of quipazine is limited due to its emetic effects via off-targets that include the 5-HT_3R - a pentameric ion channel. Here we synthesized a series of quipazine analogs with the goal of maintaining psychedelic properties via 5-HT_{2A}R while eliminating activity at the 5-HT_3R. Using [^{3}H]ketanserin and [^{3}H]LSD binding displacement and Ca^{2+} mobilization assays in HEK293 cells stably expressing 5-HT_{2A}R, our data suggest that compounds VCU-1012 and VCU-1021 exhibit affinities and potencies in the micromolar range, with an efficacy ~45% as compared to 5-HT. Volinanserin, a highly specific 5-HT_{2A}R antagonist, blocked intracellular Ca^{2+} mobilization induced by both quipazine analogs. In vivo, both VCU-1012 and VCU-1021 induced a dose-dependent effect on head-twitch behavior in C57BL/6 male mice, with VCU-1012 being more efficacious. Neither VCU-1012 nor VCU-1021 exhibit agonist activity at the 5-HT_{3A}R measured by automated whole-cell voltage clamp electrophysiology (Sophion Qube384) in a tetracycline-inducible Flp-In-293 T-REx cell line, and a mouse gut motility assay. These findings may lead to the identification of quipazine analogs not only as a new structural class of classical 5-HT_{2A}R-dependent psychedelics, but also as potential fast-acting therapeutics similar to those in clinical trials.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

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Program #/Poster #: PSTR105.10/OO8

Topic: G.09. Drugs of Abuse and Addiction

Title: Investigating the effects of serotonergic psychedelics on stress-induced anorexia

Authors: *M. FRANCIS, A. KOEHLER, W. SMITH, A. C. SMITH, E. AZEVEDO; Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Anorexia Nervosa (AN) is a debilitating eating disorder with no approved pharmacotherapies and the highest mortality rate of all neuropsychiatric disorders. The neurocircuitry of AN involves alterations in limbic and cortical circuits coding for rewarding and emotional properties of food, homeostasis, and cognitive control. Altered connectivity between the prefrontal cortex and insula has been observed in AN, as well as dysregulated serotonin and BDNF signaling. Serotonergic psychedelics have been shown to elicit rapid and sustained increases in plasticity via the 5HT2A receptor, and more recently, via positive allosteric modulation of the BDNF receptor TrkB. Psychedelics show promise as a treatment for AN, but their effects on AN's underlying neurobiological mechanisms have yet to be investigated.
We performed iDISCO+ to map whole brain activation following administration of structurally distinct 5HT2AR agonists 2,5-Dimethoxy-4-iodoamphetamine (DOI) and N, N-Dipropyltryptamine (DPT). We found that psychedelic-induced FOS expression was significantly elevated in cortical regions, including the insula. To investigate transcriptional impacts of tryptamine psychedelics, quantitative polymerase chain reaction and molecular profiling of activated neurons by phosphorylated ribosome capture (PhosphoTRAP) was performed in the insula following administration of DPT or saline. Using qPCR and Taqman assays, we found a significant increase in plasticity-related genes in the insula were observed following acute DPT administration, including BDNF. We then investigated the neurobiological effects of psychedelics in a stress-induced anorexia (SIA) model. We hypothesize that psychedelics mitigate stress-induced behavioral and neurobiological alterations in SIA. To model SIA, we exposed male and female mice to restraint stress (60 min) daily. Mice expressing an SIA phenotype were assessed using a battery of behavioral assays. Mice were treated with either DPT or saline control, and alterations in anxiety-like behavior, food intake, and body weight were compared in drug-treated and control animals. iDISCO+ was performed to map alterations in network connectivity in response to psychedelics in SIA and stress-naïve mice. In conclusion, the effects of tryptamine psychedelics on the insula, a brain region relevant to stress and feeding behavior, will shed light on the neural basis of anorexia. This preclinical study provides insights into the effects of psychedelics on dysregulated feeding and neural circuitry relevant to AN and other neuropsychiatric disorders.

Disclosures: **M. Francis:** None. **A. Koehler:** None. **W. Smith:** None. **A.C. Smith:** None. **E. Azevedo:** None.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.11/OO9

Topic: G.09. Drugs of Abuse and Addiction

Title: Changes in brain structure and function following oral exposure to LSD during adolescence in mice: A multimodal MRI study

Authors: *L. M. HARRIS[1], Z. SMITH[1], P. KULKARNI[1], D. ATHREYA[1], C. FERRIS[2]; [1]Northeastern Univ., Boston, MA; [2]Northeastern Univ. Program In Behavioral Neurosci., Northeastern Univ. Program In Behavioral Neurosci., Boston, MA

Abstract: Changes in brain structure and function following oral exposure to LSD during adolescence in mice: A multimodal MRI study
Authors: L. M. HARRIS[1], Z. SMITH[1], R.J. ORTIZ[2], D. ATHREYA[1] R. UTAMA[1] P.P. KULKARNI[1], C.F. FERRIS[1,3] [1] Center for Translational NeuroImaging, Northeastern University, Boston, MA, USA [2]Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces NM; [3]Departments of Psychology and Pharmaceutical Sciences Northeastern University, Boston, MA
DisclosuresCFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.
Abstract: Amidst the War on Drugs in 1971, the United Nations classified LSD and other psychedelic drugs as Schedule 1 substances. However, in the past decade, there has been a resurgence of scientific interest in LSD. Small clinical trials report promising results in treating MDD, end-of-life distress, PTSD, and alcoholism. How does LSD alter brain neural circuitry to affect behavior? Does exposure to LSD in adolescence have long-lasting effects on brain structure and function? To address these questions we studied male and female mice exposed to LSD during neurodevelopmental adolescence for changes in neurobiology in adulthood using multimodal MRI and behavior assays testing for motor control, cognitive function, and anxious presentation. Male and female mice (18-22 g) were exposed to vehicle (n=12), a single oral dose of LSD (n=12), or six doses spread over two weeks (n=11). All mice were given an oral gavage of 100 µl of solution, equivalent to 3.3 µg LSD. All treatments started on postnatal day 51. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the disruptions in circadian rhythms. Mice were imaged and behavior was tested at postnatal days 90 – 150 (young adulthood). Male and female mice exposed to LSD multiple times in adolescence presented with dramatic changes in gray matter microarchitecture over many brain areas as compared to vehicle and single dose mice. Resting state functional connectivity was altered in thalamocortical circuitry. When exposed to the smell of fox, a natural predator, or the smell of an innate reward, almond, the pattern of brain functional activity for multidose mice was different toward fear and reward than vehicle or single dose mice. Interestingly, there were minimal difference in cognitive or motor behaviors between groups. We

continue to study the neurobiology contributing the long-lasting changes observed in male and female mice exposed to repeated exposure to low doses of LSD in adolescence.

Disclosures: L.M. Harris: None. **Z. Smith:** None. **P. Kulkarni:** A. Employment/Salary (full or part-time):; Northeastern University. **D. Athreya:** None. **C. Ferris:** A. Employment/Salary (full or part-time):; Northeastern University. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.12/OO10

Topic: G.09. Drugs of Abuse and Addiction

Title: Dose-dependent changes in olfactory, cortical/thalamic and cerebellar activity following exposure to LSD: a BOLD MRI study in awake rats.

Authors: *A. GHAW[1], A. CHUNDURI[1], M. KOZLOWSKA[1], E. NARINSKY[1], P. P. KULKARNI[2], C. FERRIS[3];
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Abstract: Amidst the War on Drugs in 1971, the United Nations classified lysergic acid diethylamide (LSD) and other psychedelic drugs as Schedule 1 substances. However, in the past decade, there has been a resurgence of scientific interest in LSD. Small clinical trials report promising results in treating MDD, end-of-life distress, PTSD, and alcoholism. How does LSD alter brain neural circuitry to affect behavior? To address this question we used BOLD imaging to follow changes in brain activity in male and female rats exposed to LSD. Awake male and female rats were exposed to veh, 10ug/kg or 100 ug/kg of LSD during the 35 min scanning session followed by resting state functional connectivity. Images were registered to, and analyzed, using a 3D MRI rat atlas providing site-specific data on 173 different brain areas. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the transitions between the L-D dark cycles. Male and female rats exposed to the low dose of LSD (10ug/kg) showed no increase in BOLD signal, but a region-specific reduction in activity localized to the primary olfactory system and amygdala. High dose LSD (100ug/kg) produced a region-specific reduction in brain activity that included the olfactory system together with prefrontal cortex and higher order thalamic nuclei, e.g. VPL, VPM, LD, MD, and lateral geniculate. Resting state functional connectivity was altered in thalamocortical circuitry. Interestingly, only high dose LSD produced enhanced BOLD activity and only then in the

cerebellum, particularly the deep cerebellar nuclei. The reduction of sensory input through olfaction and the putative dissociation between thalamic and cortical areas with the high dose LSD may reflect the hallucinogenic effects of the drug.

Disclosures: **A. Ghaw:** None. **A. Chunduri:** None. **M. Kozlowska:** None. **E. Narinsky:** None. **P.P. Kulkarni:** 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.; Ekam Imaging. **C. Ferris:** 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.; Ekam Imaging.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.13/OO11

Topic: G.09. Drugs of Abuse and Addiction

Title: In vivo imaging of synaptic density changes in mouse using synaptic vesicle glycoprotein 2A tracer [^{18}F]SynVesT1

Authors: J. ROKKA[1], P. POUTIAINEN[2], *T. HUHTALA[1], S. BÄCK[1], **J. RYTKÖNEN**[1]; [1]Charles River Discovery Services, Kuopio, Finland; [2]Kuopio Univ. Hosp., Kuopio, Finland

Abstract: Synaptic vesicle glycoprotein 2A (SV2A) is a transmembrane protein expressed in all synaptic terminals, irrespective of neurotransmitter content (Rossi *et al.* 2022, Sec. Brain Imaging Methods). Decreased synaptic density are known to correlate with the severity and progression of multiple neuropsychiatric and neurodegenerative diseases whereas psychedelics as Psilocybin has shown to increase the synaptic density in living brain (Sadasivam et al., 2020, Mol Imaging Biol, Raval *et al.* 2021, Int. J. Mol. Sci., Toyonaga et al., 2022, Front. Neurosci). With the opportunity to measure synaptic density changes in living brain with positron emission tomography (PET), neuroimaging has taken immense leap in the following of neurodegeneration and studying treaments to prevent neuronal loss in the living brain.
In this study we established radiosynthesis for [^{18}F]SynVesT1, a PET tracer targeting SV2A, for studying synaptic density changes in rodents with PET imaging.
[^{18}F]SynVesT1 was synthetized as previously described with slight modifications (Li *et al.* 2019, ACS Chem Neurosci). In vivo PET imaging was performed with small animal PET/CT (NanoPET, BioScan) for three mice at a time under isoflurane anesthesia. C57B/6 mice were dosed 5-10 MBq intravenously. Specific binding to SV2A was confirmed by displacement with known SV2A inhibitor Levetiracetam (30 mg/kg, iv.).
[^{18}F]SynVesT1 was produced with good radiochemical purity (>99.5% and molar activity >1 TBq/µmol). Reversible binding to SV2A was observed ubiquitously in the brain. Highest radioactivity concentration was observed in thalamus and hippocampus. Interscan dosing of

Levetiracetam displaced radiotracer from the brain seen as reduced radioactivity concentration. In summary, [^{18}F]SynVesT1 was produced repeatably allowing imaging of multiple animals with the same synthesis batch. *In vivo* PET imaging of synaptic density in CNS models provides valuable tool for pre-clinical drug development and a translational method to observe development of neuro-psychiatric and neurodegenerative diseases.

Disclosures: **J. Rokka:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **P. Poutiainen:** A. Employment/Salary (full or part-time):; Kuopio University Hospital. **T. Huhtala:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **S. Bäck:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **J. Rytkönen:** A. Employment/Salary (full or part-time):; Charles River Discovery Servicess.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.14/OO12

Topic: G.09. Drugs of Abuse and Addiction

Title: Dose-dependent Modulation of brain activity by Psilocybin in mice: Insights from Functional Ultrasound Imaging

Authors: *A. SHATILLO, H. VAHERTO, R. IMMONEN, S. BÄCK;
Charles River Discovery, Kuopio, Finland

Abstract: Here we provide an insight into the neurobiological effects of the psychedelic compound psilocybin, which has been reported to have positive effects in devastating psychiatric disorders e.g., major depression or PTSD. The focus of this study was to characterize acute dose-related effects of psilocybin on the mouse brain activity, using state-of-the art imaging modality, functional ultrasound (fUS). Like fMRI, this novel, non-invasive imaging technique enables indirect measure of neuronal activity via local changes in brain perfusion.
Three groups of naive C57Bl6j animals (n=10/group) received intraperitoneal (i.p.) vehicle pretreatment prior to the imaging, followed by i.p. infusion of either vehicle or psilocybin at doses of 1 mg/kg and 2 mg/kg during a continuous fUS imaging session. Additional, 4th group, received a highly selective 5-HT2A receptor antagonist Volinanserine (MDL100907) as a pretreatment (0.1 mg/kg, i.p.) and 2 mg/kg psilocybin dosing during the scan.
Animals were anesthetized using Isoflurane for fixation and catheterization. Main physiological parameters were monitored and maintained throughout the preparation and imaging. After setup, Isoflurane was gradually switched to subcutaneous dexmedetomidine anesthesia (bolus of 0.05 mg/kg, followed by infusion 0.15 mg/kg/h). Psilocybin or vehicle was injected intraperitoneally during continuous 35 min long functional scan (5 min baseline + 30 min follow-up). Data was acquired with IconeusOne fUS system (Iconeus, Paris, France) using a 128-element probe at a frame rate of 500 Hz, covering the area from -1.5 to -0.3 mm from Bregma.
Our analysis revealed a dose-dependent reduction in cerebral blood flow (CBF) in response to

psilocybin dosing (in line with fMRI observations in humans). Particularly, we noted significant decline in fUS signal in relevant cortical (cingulate, retrosplenial cortex) and subcortical regions (striatum, hippocampus, hypothalamus), suggestive of a broad effect on brain activity. Signal change magnitude reached ~15% in 1 mg/kg and ~20% psilocybin group pretreated with vehicle. Pretreatment with MDL100907 effectively reversed the effects of high dose of psilocybin, with change not exceeding ~5% over time.
Our results illuminate the potential of fUS imaging as a powerful, sensitive tool for preclinical drug testing in the field of psychedelic research. By enabling real-time monitoring of cerebrovascular responses, it facilitates understanding of the test compound action In Vivo. Fully reversible, non-invasive dexmedetomidine protocol is stable and supports chronic fUS experiments for longer follow-up studies with multiple components and treatments.

Disclosures: **A. Shatillo:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **H. Vaherto:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **R. Immonen:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **S. Bäck:** A. Employment/Salary (full or part-time):; Charles River Discovery Services.

Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR105.15/OO13

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01MH129282

Title: Psychedelic control of prefrontal cortex excitability

Authors: *T. EKINS[1], I. BROOKS[2], S. KAILASA[2], C. RYBICKI-KLER[2], I. JEDRASIAK-CAPE[2], E. DONOHO[2], O. J. AHMED[2];
[1]Psychology, [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Serotonergic psychedelic drugs are thought to increase excitability of prefrontal cortex layer 5 pyramidal cells (PFC L5 PCs) through activation of 5-HT2a receptors, however the underlying mechanisms are largely unknown. Here, we used whole-cell electrophysiology and pharmacology to test the hypothesis that psychedelic drugs increase intrinsic and synaptic excitability of murine PFC L5 PCs (>150 neurons, adult, male/female) using graded doses of both phenethylamine and tryptamine psychedelic drugs. Consistent with earlier studies of serotonin acting on 5-HT2a receptors, we found that psychedelic drugs induced a thresholded dose-dependent increase in spontaneous glutamate release. However, psychedelics dose-dependently suppressed evoked firing. Thus, contrary to leading theories, psychedelic drugs robustly decrease intrinsic excitability of PFC L5 PCs.

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Poster

PSTR105. Hallucinogens: Neural Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.16/OO14

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NC3Rs grant NC/W00092X/1
Dstl studentship grant

Title: Determining and understanding the behavioural and physiological effects of drugs of abuse using zebrafish larvae

Authors: C. HILLMAN[1], J. KEARN[2], ***M. PARKER**[1];
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Abstract: In 2020, more than 350 million people in the world engaged in illicit drug misuse, with around 50% of the population aged 12 and above having used illicit drugs at least once. In the USA, one in five deaths among individuals aged 24 to 35 are attributed to the misuse of opioids, with almost 80% involving the use of multiple drugs, underlining the dangers that substance misuse poses to public health. Drug misuse raises an economic concern, costing the USA $78.5 billion annually. There is a pressing need to understand substance misuse at a biological level if we are to develop effective treatments and interventions to prevent some of this harm, and animal models are often used. Zebrafish larvae offer an exciting prospect, as they have the potential for a 3R's-friendly alternative to mammals, and offer the potential for high-throughput. Here, we investigated the effects of several classes of drugs of abuse on a newly validated series of light/dark assays on zebrafish (*Danio rerio*) larvae at 4 days post fertilisation (dpf). We exposed 4dpf larvae to a variety of different classes of substances of abuse and recorded their movement for three hours, including 5-min alternating light and dark. Control fish exhibited expected low movement during the light phase and increased movement during the dark phase. Exposure to low concentrations (0.5-5μM) of diazepam (Valium) induced hyperactivity during the dark phase, followed by concentration-dependent reductions in movement. These findings were replicated with other sedatives that interact with $GABA_A$ receptors, such as midazolam, flunitrazepam (Rohypnol), and sodium thiopental. No changes in locomotion were observed with gamma-Hydroxybutyric acid (GHB) exposure, which aligns with the current lack of understanding of GHB receptor characterization in fish. Ketamine and tiletamine reversed the response to light and dark, causing increased movement during the light phase and reduced movement during the dark phase (5-50 μM). Finally, opioid exposure resulted in concentration-dependent reduction in movement, suggesting comparable potencies to humans. Our findings demonstrate the predictive validity of the light/dark assay for assessing drugs of abuse from different drug classes. This assay is the first to use 4dpf larvae for validated light/dark assays of drugs of abuse, and will be used in the our future research to further investigate the effects of novel synthetic psychoactive drugs, as well as multi-substance administration.

Disclosures: **C. Hillman:** A. Employment/Salary (full or part-time):; University of Surrey, UK. 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.; Dstl (PhD funder). **J. Kearn:** A. Employment/Salary (full or part-time):; Dstl (UK). **M. Parker:** A. Employment/Salary (full or part-time):; University of Surrey, UK. 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.; 3Z pharmaceuticals, BBSRC (UK), Dstl (UK), ALSA.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.01/OO15

Topic: H.03. Decision Making

Support: CIHR Grant PJT178334

Title: Intracortical electrical microstimulation in dACC interrupts the onset of exploration

Authors: *R. SINGHAL[1], B. Y. HAYDEN[2], B. R. EBITZ[1];
[1]Univ. de Montreal, Montreal, QC, Canada; [2]Univ. of Minnesota Twin Cities, Univ. of Minnesota Twin Cities, Saint Paul, MN

Abstract: Effectively striking a balance between exploration and exploitation is crucial in navigating unpredictable and ever-changing environments. Previous studies have demonstrated a correlation between neural activity in cortical regions such as the dorsal anterior cingulate cortex (dACC) and hidden cognitive variables during tasks requiring exploration and exploitation. Although a substantial amount of information is encoded in the dACC, the causal impact of dACC perturbations on exploration and exploitation remains undetermined. To address this lacuna, we conducted an experiment integrating cortical stimulation (μ;-stim), a computational model, and large-scale neural recordings in downstream motor areas.Two rhesus macaques performed a classic decision-making task: a saccadic multi-arm bandit. At the onset of each trial, the subjects fixated on a central spot then three targets appeared. The subjects selected one of these three targets by making a saccade towards it. Targets were visually indifferent but each one was associated with a dynamic reward rate. In order to maximize the overall reward, sometimes monkeys would sample other targets despite the risk of losing immediate future rewards. We used a hidden Markov model to identify states of exploration and exploitation during the task (Ebitz, Albarran, Moore, 2018). Throughout the session, μ;-stim was randomly administered within the dACC during the inter-trial intervals (protocol after Williams, & Eskandar, 2006). This same μ;-stim was provided in the dorsolateral prefrontal cortex (dlPFC) as a control. To ascertain whether the monkeys showed any preference for stimulation, they also performed a choice task between options that were or were not paired with μ;-stim.Analysis showed that μ;-

stim in the dACC reduced the probability of transitioning into an exploration state. However, the μ;-stim did not induce any significant difference in the overall probability of exploration. The choice task revealed that the μ;-stim was not functioning as a reward. Furthermore, dlPFC μ;-stim did not alter the likelihood of transitioning into exploration. The analysis of neural recordings from downstream motor areas is still in progress. These findings suggest that perturbing neural activity with μ;-stim in dACC can interrupt the transition to the exploration state. It could suggest that activity in dACC might be causally encoding the cognitive variables required to optimally switch into the exploration state. Future work is needed to reveal how μ;-stim alters activity in dACC and disrupts the transition into the exploration state.

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Poster

PSTR106. Neural Mechanisms: Choice

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.02/OO16

Topic: H.03. Decision Making

Support: NIMH Grant R21 MH127607
Research fellowship, Jacobs Foundation
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Title: Humans forage for reward in a classic reinforcement learning task

Authors: *M. ZID[1], A. LAVIGNE-CHAMPAGNE[1], A. SHOURKESHTI[1], D. HARREL[2], A. B. HERMAN[2], B. EBITZ[1];
[1]Neurosci., Univ. de Montréal, Montréal, QC, Canada; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Suppose you are in a casino, standing before an array of slot machines, each with a different and uncertain payout that changes over time. Now, you're faced with a choice to make: which slot machine will you select to play? From the perspective of cognitive neuroscience, you should gauge the potential returns of each slot machine based on their history and then lean towards the one promising the greatest reward, modulo some exploratory noise. However, an ethologist would argue that you should have a propensity to stay with the most rewarding slot machine until the payout drops below a certain level or threshold, at which point you start exploring the others. While both hypotheses wield considerable influence within their respective fields, it remains uncertain which one best describes human decision-making. Our aim was to determine whether human sequential decision-making was better described as a compare-to-threshold process (“foraging”) or as a compare-alternatives process (“Q-learning, QL”). 258 participants (120 females, 2 other/non-reporting) performed a classic sequential decision-making task known as a restless 2-armed bandit via the Amazon mTurk platform. The task naturally encourages participants to alternate between two states: exploiting valuable options and exploring other possibilities that could prove more beneficial. The data was then used to fit both

the QL and foraging models. In addition, we modeled exploration and exploitation as the latent states underlying sequences of decisions via latent state models and interrogated the dynamics of exploration and exploitation in both models and in the participants.We found that the foraging model was a better fit for participant behavior. This model better predicted the participants' tendency to repeat choices (versus switch between options) on both individual and group level and it better captured the dynamics of their choices. Interestingly, the foraging model was also able to predict the existence of held-out participants with very prolonged repetitive choice runs, a pattern of choice that was almost impossible within the RL model.These findings indicate that the foraging model not only aligns more accurately with human behavior compared to the QL model, but also predicts salient features of behavior that cannot be described in a QL framework. Together, these results suggest that the foraging model was a better fit for the participants because it better captured the dynamics of their choices: their tendency to alternate between temporally extended periods of exploiting good options and shorter periods of exploring alternatives.

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Poster

PSTR106. Neural Mechanisms: Choice

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Program #/Poster #: PSTR106.03/OO17

Topic: H.03. Decision Making

Support: Discovery Grant #RGPIN-2020-05577
Junior 1 Chercheur-Boursier #284309)
the Jacobs Foundation (Research Fellowship)

Title: A comparative study of exploratory decision-making differences in mice, monkeys and humans

Authors: *V.-J. LAURIE[1], A. SHOURKESHTI[1], C. S. CHEN[2], B. A. EBITZ[1];
[1]Dept. of Neurosci., Univ. de Montréal, Montréal, QC, Canada; [2]Dept. of Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: The survival and competitiveness of living species depend on their ability to optimise rewarding decisions. In a complex, changing environment, decision-makers are faced with a conundrum: should they continue to exploit an already rewarding option or should they explore new alternative options? While exploiting is immediately rewarding, it poses the risk of overlooking potential better options. Exploring is more uncertain, but through this process, species can sample alternative paths, learn about their environment, and enhance their potential for future rewards. Although all species face this conundrum, variations in brain structure, function, and behavioural ecologies could set a different optimal balance between exploration

and exploitation for each species, favouring a different "decision-making strategy". This project tested the hypothesis that different species adopt different decision-making strategies in an explore/exploit task. Mice, monkeys, and humans performed a classic explore/exploit task known as a restless multi-armed bandit. In this task, species were presented a series of trials where they had to make choices between physically identical targets. Each target offered a probability of reward which changed independently over time. In consequence, all species were incentivized to both exploit rewarding options and occasionally explore alternative options. While we observed similar levels of performance across species, mice reached this level of performance via a different strategy than primates. Mice switched options more frequently. To delve into differences in exploration and exploitation across species, we used a hidden Markov model to identify latent explore and exploit states during the task (Chen et al., 2021; Ebitz et al., 2018). The model revealed that mice explored more than both primates. Analyses of model dynamics suggested that mice were less likely to persist in exploitation, compared to primates. A variety of control experiments ruled out low-level explanations for these species' differences. These findings suggest that mice may differ from primates in how they explore uncertain environments. This could potentially be due to species-specific variations in intrinsic neural timescales, which impact information processing (Golesorkhi et al., 2021; Murray et al., 2014; Zilio et al., 2021) and could affect the duration of exploitation. We speculate that species differences in decision-making strategies may be linked to variations in their behavioural ecologies. Ultimately, this study enhances understanding of the similarities and differences between animal and human cognition.

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Poster

PSTR106. Neural Mechanisms: Choice

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Program #/Poster #: PSTR106.04/OO18

Topic: H.03. Decision Making

Support: NSERC Discovery: RGPIN-2020-05577
Jacobs Fellowship
FRQ - Santé: 295755

Title: Overt attentional strategies during multi-dimensional value-based decision-making

Authors: *D. H. KEHOE[1], M. BOURGON[2], B. EBITZ[3];
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Abstract: We live in an uncertain world where some choices are more rewarding than others. Very often, an option's visual features indicate its reward value (e.g., color may predict taste). Visual features can thus guide our decision-making processes, as we learn to associate them with

reward. However, when options have multiple features that interact to determine value, the number of associations that must be learned and remembered increases exponentially. In this context, it seems likely that decision-makers would need to implement some kind of simplifying strategy to guide their choices to the best option. Here, we sought to determine if this is the case by looking at how overt visual attention changes as a function of learning in a multi-dimensional value-based decision-making task. In our experiment, humans made a series of decisions in a dense visual environment made up of options with color and orientation feature conjunctions. Critically, because our task dissociated overt attentional selection (saccades) from the final choice (button press), we could separate the exploration strategies used to investigate options from the strategies that guided the economic choice. Each option's unique combination of features determined its level of reward and reward-feature contingencies occasionally and unexpectedly changed. The change points allowed us to determine how people explored this complex environment both when they understood the feature associations, and when they were learning them. In a preliminary sample of 10 participants, we observed a few intriguing results. First, we found that participants consistently investigated *more* options after the change points than before. Follow up work will determine whether this is because they continued to have an attentional bias towards previously rewarded options or if they were simply more interested in evaluating more options when they were uncertain. Participants also had biases for both color and orientation, but surprisingly, these biases were not maximal at the change points, but instead most obvious when the participants had already committed to a target. We speculate that this could be due to a censoring process in which participants were *only* able to successfully find the correct target when it was aligned with pre-existing biases. Additional analyses will detail (1) the strategies participants use to visually explore the feature space during periods of both certainty and uncertainty, (2) the factors that determine when participants will switch between these strategies, and (3) how previously learned associations influence subsequent decisions, be those decisions attentional or economic.

Disclosures: D.H. Kehoe: None. **M. Bourgon:** None. **B. Ebitz:** None.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.05/OO19

Topic: H.03. Decision Making

Support: NIH Grant MH119391

Title: Lateral habenula inactivation with muscimol impairs strategy switching on a complex cognitive flexibility task

Authors: *V. HONES, M. BOTTOMS, G. MULLINS, T. T. TRAN, S. J. Y. MIZUMORI; Univ. of Washington, Seattle, WA

Abstract: The lateral habenula (LHb) is an epithalamic structure that largely consists of excitatory glutamatergic neurons. Previous research from our lab has found that LHb inhibition with muscimol resulted in decreases in behavioral flexibility (Baker et al. 2019). Another study has shown that LHb inhibition impairs the ability to disengage from pre-established tasks (Sleezer et al. 2021). These findings suggest that the LHb plays a role in flexibly updating current rules to inform future actions. Using a more stringent test of behavioral flexibility that specifically assesses flexibility in the use of different strategies, this experiment tested the LHb's role in a more complex behavioral flexibility task that requires strategy-switching. Here, Long-Evans rats (N=2 so far) were pre-trained on a strategy-switching task, then bilaterally implanted with cannulas targeting the LHb. The strategy switching task was performed on a fully automated plus-maze and consisted of 2 strategy types: place and alternation. The task required the rats to complete 12 correct responses out of a sliding 15-trial window in order to move on to the next strategy block (resulting in a maximum of 4 strategy blocks, or 3 strategy switches, in a session). The experimental timeline consisted of a baseline day (no infusions) followed by either muscimol (35ng/250nl, 0.07µl/min) or saline infusion in counterbalanced order. We hypothesized that LHb inactivation would impair the rat's ability to update choice behaviors according to changing task rules which would prevent accurate strategy switches. Our preliminary results show that LHb inactivation resulted in decreased completed blocks and fewer correct choices per session. Importantly, these effects are equally distributed across both strategies. Trials to complete a block and perseverative errors did not reach statistical significance. These results cannot be readily explained by impaired sensorimotor processing or reduced motivation. These data support earlier research suggesting that the LHb plays a role in updating rules to inform future behavioral flexibility perhaps by facilitating the use of different task strategies. Future research should aim to elucidate the specific contributions of individual subpopulations within the LHb to flexible decision-making.

Disclosures: **V. Hones:** A. Employment/Salary (full or part-time):; University of Washington. **M. Bottoms:** None. **G. Mullins:** None. **T.T. Tran:** None. **S.J.Y. Mizumori:** A. Employment/Salary (full or part-time):; University of Washington.

Poster

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.06/OO20

Topic: H.03. Decision Making

Support: NIH Grant MH119391

Title: Behavioral flexibility and its relationship to hippocampal-prefrontal dynamics during spatial set shifting

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Abstract: Rodents occasionally vacillate between options when making decisions. Prior work has suggested that this behavior, known as vicarious trial and error (VTE), is modulated by strategy use, task demands, and task proficiency. Using a spatial set shifting task that requires rats to flexibly switch between: A) contingencies where rewards are continually delivered in the same location; and B) a contingency where rewards alternate between locations, we show that VTE rates are not tied to utilization of a particular strategy. Instead, using recency-weighted Bayesian inference to estimate when subjects learn rewarded contingencies, we show that VTE rates change as function of learning and with respect to task demands. Additionally, we show that hippocampal-prefrontal theta coherence varies on long, multi-trial timescales during this task, while beta coherence between structures displays stronger sub-trial temporal alignment to decision-making. Ultimately, we seek to understand whether variations in behavioral flexibility are related to changes in hippocampal and/or prefrontal dynamics, or whether these dynamics fluctuate largely independently of trial-by-trial behavioral variability.

Disclosures: **J.T. Miles:** None. **G.L. Mullins:** None. **S.J.Y. Mizumori:** None.

Poster

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Support: Burroughs Wellcome Fund CAMS
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NIMH L40MH127601

Title: The ability to hoard food while foraging on a neuroeconomic task diminishes choice conflict during deliberation

Authors: *C. A. NWAKAMA[1], R. DURAND-DE CUTTOLI[2], J. E. HALLER[5], J. L. ABLES[3], B. M. SWEIS[4];
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Abstract: The delivery of food often serves as the primary reinforcer in operant tasks. Reinforcement of reward-seeking behavior when tested on more naturalistic tasks, including foraging paradigms, may change numerous aspects of appetitive motivation mediated by different neural circuits. Thus, it is important to understand the complex relationships between task structure and an animal's environment when examining interacting elements that may influence choice behavior. The ability to hoard food is one aspect that has been studied in the

traditional foraging and behavioral ecology literature but seldom in decision neuroscience. Here, we examined the effects of hoarding on decision-making behavior in mice tested on a neuroeconomic foraging task. 20 10-week-old CB57BL/6J male mice were tested on the "Restaurant Row" spatial decision-making task. Mice foraged daily for their primary source of food while on a limited time budget. Mice were allotted 45 min to traverse a square maze with four uniquely flavored feeding patches, or "restaurants," for which mice display subjective preferences. Each restaurant had unique spatial cues and a separate offer zone and wait zone. Upon entry into an offer zone, a tone sounded whose pitch indicated the delay mice would have to wait to earn a 20 mg food pellet should they choose to enter the wait zone. Pellets were delivered via a custom-designed 3D-printed modular dispenser. This device includes a programmable trap-door mechanism designed to discard earned food pellets that were not retrieved. 10 mice were randomly assigned to undergo testing with the trap-door feature inactivated (TI group). Since mice do not always immediately retrieve earned pellets, this manipulation allowed us to examine the effects of hoarding on behavior. Both groups earned similar amounts of food at matched body weights. TI mice spent more time at the reward sites. Interestingly, this stemmed from both time engaged in as well as outside of the task structure, consistent with TI mice consuming hoarded food. When examining choice behavior in the offer zone, we measured vicarious trial and error (VTE) behavior, a metric of the absolute integrated angular velocity, or physical hemming and hawing, of path trajectories. We previously demonstrated VTE increases as animals develop planning strategies and is a correlate of neural signatures of on-going deliberation. Surprisingly, we found that TI mice displayed diminished VTE behavior. These findings suggest the ability to hoard food while foraging may change the perception of reward scarcity in the environment and lead to different decision-making evaluations, including computations involved in choice conflict.

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Poster

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Program #/Poster #: PSTR106.08/OO22

Topic: H.03. Decision Making

Title: Diabetes alters economically dissociable decision-making algorithms depending on the salience of reward scarcity in the environment

Authors: C. A. NWAKAMA[1,2], R. DURAND-DE CUTTOLI[1], Z. M. OKETOKOUN[3], S. O. BROWN[4], J. E. HALLER[5,3], A. MENDEZ[1], M. JODEIRI FARSHBAF[3], Y. Z. CHO[3,6], S. AHMED[1,7], S. LENG[3,8], **J. L. ABLES**[3,1], B. M. SWEIS[3,1];
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and Sci., Scranton, PA; [6]Dept. of Chem., Barnard Col. of Columbia Univ., New York, NY; [7]Macaulay Honors at CUNY Hunter, New York, NY; [8]Hunter Col. High Sch., New York, NY

Abstract: Those with diabetes mellitus are at higher risk of developing depression and other psychiatric disorders. Although diabetes is primarily characterized by chronic hyperglycemia, it remains unclear how impaired insulin function, which is known to have direct effects on neural activity, regulates motivated behavior.
We characterized value-based decision-making of an insulin-deficient diabetic mouse model on a naturalistic neuroeconomic foraging paradigm. 40 8-week old CB57BL/6J male mice were injected with either vehicle (VEH) or streptozotocin (STZ), an antibiotic that ablates insulin producing beta cells in the pancreas, to induce hyperglycemia. Mice were then tested across two months on the "Restaurant Row" task during which they foraged daily for their primary source of food while on a limited time budget. Mice learned to make serial decisions accepting or rejecting reward offers as a function of cost (delays cued by tone pitch) and subjective value (flavors cued by unique spatial contexts).
Mice were trained on two different schedules during which the economic landscape (i) drastically or (ii) gradually progressed into an increasingly reward-scarce environment. Overall, STZ-treated mice earned less food but shifted meal consumption patterns in complex ways based on the revealed preferences of various flavors. Vicarious trial and error behavior, a proxy of deliberation, revealed decreased decision conflict for less-preferred flavors in STZ-treated mice. These findings were divorced from individual differences in economic choice policies, which were uniquely modulated in STZ-treated mice depending on their prior training schedules. Interestingly, we found that groups of mice valued the passage of time differently based on the type of choice being made. During change-of-mind decisions, mice became sensitive to the magnitude of time spent waiting, or "sunk costs," in altering the probability of earning a reward but only after transitioning into a reward-scarce environment - except STZ-treated mice trained on a gradual schedule, who surprisingly never developed sensitivity to sunk costs.
Deliberative and re-evaluative choice algorithms, which have been previously shown to be processed in physically separable circuits in the brain, may be differentially perturbed in a mouse model of insulin-deficient diabetes. These findings suggest that complex relationships between glycemic regulation, the contrast of realized scarcity of the environment, and different types of opportunity costs interact to influence dissociable decision-making systems and fundamentally distinct behavioral computations underlying unique aspects of reward value.

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Poster

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Topic: H.03. Decision Making

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NIMH R01MH104559
BBRF NARSAD Young Investigator Grant 31140

Title: Linking Brain-Wide Activity Patterns during Neuroeconomic Decision Making to Aggression

Authors: B. M. SWEIS[1], A. V. AUBRY[2], L. LI[2], J. SACKEY[2], F. YASMIN[2], S. O. ELHASSA[2], S. AHMED[2], E. J. NESTLER[2], S. J. RUSSO[2], ***R. DURAND-DE CUTTOLI**[2]; [1]Dept. of Psychiatry, [2]Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Aggression is an evolutionarily conserved response to a perceived threat that spans a large range of diverse behaviors, including those that may be adaptive and protective as well as those that may be pathological and dangerous to others. Circuits recruited during the expression of aggression, in addition to circuits known to subserve social interactions themselves, are critical nodes of the brain's reward system. However, it is unclear how pathological aggression may “hijack” key reward circuits in the brain, contributing to maladaptive reinforcement of aggression. Because the brain has evolved to use multiple decision-making systems, simple tests of reward value may be unable to access computational subtleties that may be altered in the brains of aggressive individuals. We characterized decision-making profiles of 40 outbred Swiss Webster mice screened for aggression and then tested on the neuroeconomic task, “Restaurant Row.” Mice had limited time each day to forage for their sole source of food investing in rewards of varying costs (delays from 1-30s signaled by tone pitch) and value (unique flavors tied to four spatially cued locations). On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene. We found that the majority of brain regions revealed decreased levels of c-Fos expression in highly aggressive animals versus non-aggressive animals. Using an unbiased, open-ended analysis approach, top region hits revealed strong negative correlations between aggression and c-Fos expression, regions that lie in the medial wall of the prefrontal cortex (mPFC) (including the anterior cingulate, prelimbic, and infralimbic cortex) and are known to be engaged by the Restaurant Row task. Using this approach, we also found that several regions across the limbic system covaried with numerous key metrics from the Restaurant Row task, suggesting specific regions may be interacting in order to give rise to complex decision-making profiles. Using a focused analysis, we found that individual differences in subjective value covaried with c-Fos expression in the mPFC, scaled along its dorsoventral axis. These data reveal how brain-wide studies of aggression may reveal changes in circuits affecting only certain types of decision being processed. These findings set the stage for future experiments manipulating circuit-specific computations, including within functional subregions of the mPFC, in order to augment multiple valuation algorithms underlying aggression.

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Poster

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Title: Sensitivity to distinct types of regret recruits separate striatal networks

Authors: R. DURAND-DE CUTTOLI[1], A. AUBRY[1], L. LI[2], J. SACKEY[1], F. YASMIN[1], S. ELHASSA[1], S. AHMED[1], E. J. NESTLER[4], S. J. RUSSO[1], ***B. M. SWEIS**[3];
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Abstract: Regret describes recognizing that an alternative action could have led to a better outcome. Recently, we discovered that there may exist fundamentally distinct types of regret processed in separable circuits. These types are defined by specific actions that lead to unique economic violations. Regret-related computations involve the integration of multiple information streams and as such, large-scale neural data is necessary to fully grasp the breadth of how several circuits converge in order to drive complex behavior. Here, we leveraged brain-wide activation data to discover pathways encoding complex decision variables and harnessed the power of unbiased imaging data to reveal circuits implicated in counterfactual thinking. We characterized 40 outbred Swiss Webster male mice on the neuroeconomic task, “Restaurant Row.” Mice had 45 min to forage for their daily source of food investing in rewards of varying costs (delays, 1-30 s signaled by tone pitch) and value (unique flavors). As previously published, regret trials were characterized by economic violations following atypical decisions either to reject high-value offers (type 1) or accept low-value offers (type 2). Immediately following these decisions, when mice were subsequently presented with low-value offers on the next trial (read-out trial), we measured regret-related behavioral sensitivity as the change in choice probability on the read-out trial relative to non-violation sequences. On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene. Brain harvesting was timed to task engagement and normalized to mice who did not perform the task but were equally food restricted and post-prandial. We found a wide range of individual differences in regret

sensitivity. We found sensitivity to type 1 vs. type 2 economic violations was negatively correlated. PCA analysis found that 78.4% of variance was explained by PC1 with mice that were most sensitive to either type 1 or type 2 scenarios occupying opposite ends of this spectrum. iDISCO+ revealed that the most robust bidirectional change in c-Fos+ cell counts was found in the amygdala (increased in type 1 / decreased in type 2 sensitive mice). This was strongly correlated with accumbens activation in type 1 sensitive mice only. In contrast, orbitofrontal and hippocampus activation was strongly correlated with accumbens activation in type 2 sensitive mice only. These data implicate the involvement of multiple regions in dissociable roles of action-specific forms of counterfactual thinking.

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Poster

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Title: Male-biased behavioral sequence variability induced by psychostimulants in a mouse model of 16p11.2 hemideletion

Authors: *E. M. GIGLIO, D. M. MUELLER, G. ROJAS, N. GRISSOM;
Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: Neurodevelopmental disorders like autism spectrum disorder (ASD) have strong male biases in diagnosis, but the underlying mechanisms controlling interactions between sex differences and genetic variation remain unclear. A key diagnostic feature of ASD is the development and expression of stereotypic motor behaviors, which employ the same neural systems involved in social and non-social reward learning. We use a mouse model of human 16p11.2 hemideletion (del/+) - a copy number variation linked to neurodevelopmental diagnoses including ASD - to delve into these interactions. 16p11.2 del/+ mice have previously been demonstrated to have changes in their striatal molecular function and learning deficits as well as sex-divergent deficits in motivational behaviors. Dopaminergic signaling is involved in repetitive locomotor behavior, motivation, and decision-making, and amphetamine locomotor sensitization is a well-established paradigm of probing dopamine function. Previous pilot data shows us that male del/+ mice rotate rapidly in response to increasing doses of amphetamine, whereas male wildtypes sensitize through increased gross locomotion. Additionally, female and male mice of

both sexes sensitize to amphetamine at different rates and doses. Here we investigate both the time scale and specific expression on sex- and genotype-specific response to amphetamine sensitization using pose estimation software (SLEAP). Preliminary results suggest there are significant reductions and/or imbalances in dopamine function in the striatum which could drive the expression of stereotypic/repetitive behaviors and bias reward guided behaviors. These results have important implications for the role of dopamine in regulating reward guided learning and decision-making in a mouse model of 16p11.2 del+/.

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Poster

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Topic: H.03. Decision Making

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Title: Nucleus accumbens dopamine signatures of decision making in a 16p11.2 hemideletion mouse model

Authors: *M. MERFELD[1], C. CHEN[1], B. EBITZ[2], N. GRISSOM[1];
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Abstract: 16p11.2 hemideletion is a copy number variant associated with neurodevelopmental conditions such as ADHD and autism. Such conditions are known to impact executive function, reward learning, and striatal function, but these impacts differ across sexes. In particular, 16p11.2 hemideletion has been found to have sex-biased impacts in both humans and mouse models. Collectively, these data raise the question of how sex modulates the influence of autosomal gene variants on reward processing and striatal dopamine neurobiology. To explore the sex-modulated impacts of 16p11.2 hemideletion (16p del), we used a mouse model of this gene variant on an F1 C57Bl6/j x 129s and trained male and female wild type and 16p del mice (8 16p del females, 7 wild type females, 11 16p del males, 10 wild type males) to perform a two-armed restless bandit task. This is a reward-guided probabilistic decision-making task where reward contingencies for two options change independently and randomly throughout a session. This task allows for comparison of neural signals for choices controlling for reward, and signals related to reward controlling for the animal's choice. It also is amenable to computational modeling approaches to uncover latent neurobehavioral states defined by sequences of choices. These include a hidden Markov model to define states of exploration, where an animal samples options to gain information, and exploitation, where an animal repeatedly selects a single option to maximize reward, as well as reinforcement learning models. In our preliminary results, we replicate a previous finding that male mice spend more time in exploration states than do female

mice. We also see preliminary evidence that transitions between explore and exploit states are impacted by 16p del. During restless bandit testing, animals also experienced concurrent dLight fiber photometry to examine dopaminergic signaling in the nucleus accumbens core (NAcc). Analysis is ongoing to determine if sex and genotype interact to impact real-time levels of dopamine in the NAcc during decision making. These results will inform us how an autosomal gene variant may impact striatal signaling in a sex-biased way in real time.

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Poster

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Doctoral Dissertation Fellowship, University of Minnesota
APA Dissertation award, American Psychological Association

Title: Distinct dopamine signatures encode state-based learning during exploration and exploitation

Authors: *C. CHEN[1], M. MERFELD[2], D. MUELLER[3], E. KNEP[4], N. M. GRISSOM[4]; [2]Elliott Hall, [3]Univ. of Minnesota, Twin Cities, [4]Univ. of Minnesota, [1]Univ. of Minnesota, Minneapolis, MN

Abstract: In uncertain environments, we must decide between two goals: exploring new information or exploiting existing knowledge of rewarding options. Since the goal of exploration is information seeking and the goal of exploitation is reward-maximizing, the reward learning during these two states should be different. Indeed, our previous study showed evidence that reward learning was elevated during exploration in mice (Chen et al., 2022). One neuromodulator well posited to modulate reward learning and exploration is dopamine. Dopamine projection to the ventral striatum is proposed to encode reward prediction error (RPE), which facilitates reward learning. Past research has implicated tonic dopamine in modulating exploration. However, it is not clear whether there are distinct signatures of dopamine transmission associated with rewarding learning during exploration and exploitation. To address this question, we trained wildtype mice (n = 22, 11 per sex, strain B6129SF1/J) to perform a two-armed restless bandit task, where the reward probability associated with each choice changed independently and randomly over time. The dynamic reward contingencies naturally

encouraged the constant transition between exploitation and exploration. During the task, we recorded dopamine efflux in the nucleus accumbens core (NAcc) with the fluorescent dopamine sensor dLight 1.3b using fiber photometry. To identify when animals were exploring, we fit a Hidden Markov model (HMM) that infer exploration and exploitation as latent goal states underlying choices. Based on our previous model validation work, the model produced robust trial-by-trial labeling of the explore/exploit state, which allowed us to examine how dopamine signals changed across those states on a trial basis. We found that reward learning was elevated during exploration - animals were more likely to stay with the same choice if rewarded and switch if not rewarded. We also discovered that dopamine responses to both rewarded and non-rewarded cues were more pronounced in the nucleus accumbens core during exploration state, compared to exploitation. This result cannot be fully explained by the classic RPE framework, because we would expect to see more negative RPE in response to not getting a reward during exploitation, due to the higher expectation of reward during exploitation. This result is more consistent with differential state-based learning, where exploration is a state of elevated learning. Together these results provide neural evidence of state-based reinforcement learning during exploration and exploitation and can inform future reinforcement learning model architecture.

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Poster

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Topic: H.03. Decision Making

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Title: Individual differences in explore-exploit behaviors predict broad autism phenotypes in general population

Authors: *E. KNEP[1], X. YAN[2], C. CHEN[1], S. JACOB[3], B. EBITZ[4], N. GRISSOM[1], A. B. HERMAN[1];
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Abstract: Autism spectrum disorder has generally been found to be associated with altered decision making, but it is unclear whether different measures of decision making vary independently across diagnostic domains within the autism spectrum. We capitalized on a well-validated community measure for autism-related phenotypes, the Broad Autism Phenotype Questionnaire (BAPQ), to examine in a large sample whether different subscales in this measure (aloof, rigid, and pragmatic language use) show shared or distinct relationships to decision

making performance measures in a probabilistic bandit task. We recruited 1001 participants through the online Prolific platform and conducted a three-armed restless bandit task. In this task, subjects were presented with three cards, each associated with some reward probability that changed independently and randomly over time. Subjects maximized the points earned by balancing the exploitation of a known rewarding choice and the exploration of potential better alternatives. We then fit a Hidden Markov model (HMM) to infer exploration and exploitation as latent states underlying choices and examined the frequency of exploratory trials. We discovered that the level of exploration is strongly associated with the aloof subscale, which primarily describes social behavior-related phenotypes. The aloof subscale also predicted outcome sensitivity, which is measured by the probability of switching in response to previous outcome feedback. To examine which specific measures best predicted individual differences in the level of exploration, we conducted a canonical correlation analysis and discovered that the strongest loading for these non-social reward related measures, including level of exploration, outcome sensitivity, and behavioral stickiness, are in fact socially coded items. These findings suggest that different aspects of decision making and decision making strategies may be related to different phenotypic domains of autism spectrum disorder, and that social components of autism spectrum disorder produce measurable differences in cognitive tasks.

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Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.15/PP4

Topic: H.03. Decision Making

Support: NIH Grant P50MH119569
NIH Grant R01MH123661
NIH Grant T32MH115886

Title: The precision of motor actions is sensitive to explore-exploit state.

Authors: *D. MUELLER[1], E. M. GIGLIO[1], C. CHEN[1], A. HOLM[1], B. EBITZ[2], N. GRISSOM[1];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. de Montréal, Montréal, QC

Abstract: In bandit decision making tasks, the challenge of sampling between options versus settling on a currently best option is better known as the explore-exploit tradeoff. Across species, there is substantial evidence that explore and exploit can be defined as neurobehavioral states using a hidden Markov model (HMM) approach. Using a restless bandit task, in which the reward probability of each choice changes randomly and independently across trials, we see that animals enter self-initiated periods of exploration and exit these to begin exploiting an option. In

mice, the use of touchscreen chambers allows us to record precise locations for each mouse touch, allowing us to consider detailed information about how decisions translate into physical motion. Transitioning between explore and exploit states could be considered as an online change in cognitive flexibility, which may be reflected in motor and behavioral flexibility. We took advantage of the data on touch locations to test whether individual trials labeled as exploit by our HMM are accompanied by more stereotyped motor behaviors in choice selection than the same choices during explore states. Thirty-two 129/b6j F1 mice (16 male and 16 female) were tested on restless bandit schedules. Previous work from Grissom lab has shown sex differences in the explore/exploit tradeoff, where males explore significantly more than females, even though both sexes complete the task equally well by acquiring the same amount of reward. Given that male and female mice employ different strategies through the restless bandit task, we began to question whether the motor movements associated with state-defined choices also look spatially different in the chamber. By employing both Euclidean and Mahalanobis analyses we find that successive touches to the same choice are further apart while an animal is in an explore state than in an exploit state, suggesting greater motor stereotypy when exploiting an option. Further, we have also found sex differences in the area of nosepoke coordinates, suggesting that males in an explore state interact with a larger area of the touchscreen than females in the same state. Additionally, preliminary data suggests that there is an impact of reward on the distance between successive touches, indicating spatial adjustments immediately following trial by trial feedback. This novel analysis capitalizes on the hidden potential for touchscreens to inform not only choice behaviors but the motor actions that generate them, and the neural states that unite movement and cognition.

Disclosures: D. Mueller: None. **E.M. Giglio:** None. **C. Chen:** None. **A. Holm:** None. **B. Ebitz:** None. **N. Grissom:** None.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

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Topic: H.03. Decision Making

Support: NIH R25DA057802
NIH P50MH119569
NIH T32MH115886

Title: Alterations in decision making in mice following CRISPR-mediated ablation of NMDA receptors in medial prefrontal cortex

Authors: A. VELOSA[1], D. MUELLER[2], R. DICK[2], E. KNEP[2], B. EBITZ[3], P. ROTHWELL[2], ***N. GRISSOM**[2];
[2]Psychology, [1]Univ. of Minnesota, Minneapolis, MN; [3]Univ. de Montréal, Montréal, QC

Abstract: Understanding the etiology of cognitive symptoms in schizophrenia is important because these are the most significant for quality of life but there are no medications aimed at treating them. System-wide NMDA receptor antagonists have been shown to produce psychosis-like phenotypes in non-human primates, mice, and humans. Frontal cortex has long been a high-priority target in understanding schizophrenia, and it is assumed that the effects of NMDA receptor antagonists are due to their effects on frontal cortex function, an untested hypothesis. To address this hypothesis, we examined the impact of CRISPR-mediated NMDA receptor ablation in the medial prefrontal cortex on mouse cognition. A key translational method for assessing cognition across mice and humans is a bandit decision making task, where the reward probability of multiple items changes independently and randomly from each other. A key measure is the balance between exploration behavior, switching choices to sample outcomes, versus exploitation behavior, staying on one choice. Explore-exploit balance has been repeatedly seen to be altered in schizophrenia and psychosis. To determine if altered explore-exploit balance is caused by NMDA receptor dysfunction in PFC, we ablate the obligate GluN1 subunit, coded by the GriN1 gene, of the receptor via cre-dependent activation of CRISPR-CAS9 in the mPFC. 8 cas9-knockin b6j mice (5 GriN1 experimental virus and 3 LacZ control virus) were tested on restless bandit schedules and 10 weeks of viral expression occurred. Preliminary results show that GriN1-deletion mice are able to complete the task, but show reductions in switching behavior, choosing between items, that is necessary for exploration. Further work will establish if the explore-exploit balance is itself shifted and whether this changes over expression of the virus. In the end, this novel viral application and combination with a bandit task can help us see if NMDA receptor hypofunction is important for the etiology of schizophrenia.

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Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.17/PP6

Topic: H.03. Decision Making

Support: NIH: DA046375-01A1
NSF 1948181

Title: Choice information develops in rat medial frontal cortex during the initial acquisition of a visually guided decision making task

Authors: *S. WHITE, M. LAUBACH;
American Univ., Washington, DC

Abstract: Studies of decision making typically use extensively trained animals. The impact of initial learning on decision making behavior and the underlying neural computations have not

been investigated. Here we evaluated neural activity related to decision making as rats made choices for the first time and over initial learning. We trained male rats to respond to one of two visual cues, predictive of either a high or low value sucrose reward. These cues were present, one per trial, over lateralized nosepoke ports randomized by left or right. After three weeks of training with these single offer trials, rats were implanted with chronic microwire arrays targeting the prelimbic cortex. Then these rats were tested with access to both cues simultaneously (one over each lateralized port) on 1/3 of trials. This allowed us to examine neural correlates of decision making for the first time. Rats showed increased response latencies (indicative of deliberation) for dual-offer compared to single-offer trials. Deliberation was robust in the first testing session and persisted over multiple test sessions. We found single units were modulated during the period of decision making. The firing rates of many of these cells (~25%) varied with the directions of the rats' responses. These cells either fired at different rates for left vs. right responses or fired exclusively on contralateral responses. Decoding methods found neuronal activity could be used to predict choices (response location). To understand the effects of increased latencies on neural activity, we trained classifiers to discriminate choices using single-offer trials and tested this classifier on dual-offer trials. Prediction accuracy of the rats' responses decreased over testing sessions for single offer, but not dual offer, trials. We calculated the difference between prediction accuracies from single and dual offer trials to measure selectivity of the neurons to encoding single-offer "forced" responses and choices between stimuli on dual offer trials. In the first test session, neurons better predicted forced responses compared to choices. This effect changed with learning. By the third test session, choices were better predicted than forced responses. These findings suggest that the neural encoding of choice information changes with learning, and studies that measure choice-related neural activity in extensively trained animals may underestimate the effects of choice on brain and behavior.

Disclosures: S. White: None. **M. Laubach:** None.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

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Program #/Poster #: PSTR106.18/PP7

Topic: H.03. Decision Making

Support: NIH: DA046375-01A1
NSF 1948181

Title: Prelimbic cortex controls the speed, but not the accuracy, of simple visually guided decisions

Authors: *J. PALMER, K. CHAVEZ LOPEZ, S. WHITE, M. LAUBACH;
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Abstract: Intra-cortical pharmacology and computational modeling were used to examine motivational and cognitive measures of decision making in a rodent model. Using a task reported in Swanson et al. (eNeuro, 2021), male and female rats were trained to select lateralized visual stimuli after responding in a central port, and the luminance of the stimulus was predictive of reward magnitude. We found a sex difference in the initial learning of the task, with female rats responding more selectively and faster to high value stimuli. ExGauss modeling of response times revealed that the Gaussian "sensorimotor" component (mu) is consistently lower in females and the exponential "noise" component (tau) decreases for males, but not females, with learning. Drift diffusion models found evidence for lower drift rates in females, and both threshold and non-decision time decreased over sessions in males but not females. These findings suggest that males improve their performance of the task as they gain more experience, while females require less evidence to choose between stimuli and have lower decision noise that remains stable throughout learning. To understand the role of the frontal cortex in this task, rats were implanted with bilateral cannula targeting the prelimbic cortex (PLC) and received infusions of the GABA-A receptor agonist muscimol (0.01-1.0 μg/μl). Reversible inactivation of PLC had motivational effects on performance, reducing choice latencies without affecting choice accuracy. ExGauss modeling found that both the Gaussian and exponential components of the response times decreased with increasing concentrations of muscimol, in both males and females. Drift diffusion modeling revealed that in males only, threshold and non-decision time decrease with increasing concentrations of muscimol. As there are currently very few studies on the role of the opioid system in the frontal cortex, we then made infusions of the mu opioid receptor agonist DAMGO (1 μg/μl) to determine how stimulating opioid receptors in PLC might impact decision making. We found that DAMGO had the opposite effects of reversible inactivation: increased choice latencies and no effects on choice accuracy. In both males and females, ExGauss modeling revealed DAMGO increased the Gaussian component of the response times but had no effects on exponential variability. Drift diffusion models showed evidence for increased thresholds and non-decision times under intra-PLC DAMGO. Together, these studies suggest that inactivating PLC reduces the amount of sensory evidence and sensorimotor preparation necessary to make a decision, while stimulating the cortical opioid system has the opposite effects.

Disclosures: **J. Palmer:** None. **K. Chavez Lopez:** None. **S. White:** None. **M. Laubach:** None.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR106.19/PP8

Topic: H.03. Decision Making

Support: CIHR Grant PJT-162312

Title: The muscarinic receptor subtype M4 improves decision making and reduces impulsivity in rats

Authors: *G. BETTS;
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Abstract: Neuropsychiatric disorders are characterized by impaired decision making and heightened impulsivity. The muscarinic system, specifically subtypes M1 and M4, plays a crucial role in these cognitive processes. This study aimed to investigate the effects of subtype-selective pharmacological modulation of muscarinic receptors on decision making and impulsivity using the cued rat gambling task. Male and female Long Evans rats (n = 32) received xanomeline (M1/M4 agonist), VU0152100 (M4 positive allosteric modulator), or pirenzepine (peripherally-acting M1 antagonist) before task performance. Behavioral measures of impulsivity, motor response, and decision making were assessed. Our findings demonstrated that xanomeline reduced impulsivity but was accompanied by a motor slowing effect. Pirenzepine had similar motor slowing effects without altering impulsivity. VU0152100 had a bidirectional impact on impulsivity in females but not males: highly impulsive females became less impulsive, while less impulsive females became more impulsive. Notably, VU0152100 promoted advantageous decisional behavior in high-impulsivity rats, with high-impulsivity males shifting from risky to safe choices following a loss, and high-impulsivity females displaying a decreased shift from safe to risky choices. These results suggest that targeting M4 may be beneficial for alleviating decisional deficits and attenuating impulsivity, specifically in clinical populations where impulsivity is elevated. Muscarinic subtype modulation, with a particular focus on M4, shows promise as a therapeutic approach for addressing cognitive symptoms in neuropsychiatric disorders. Further research is required to uncover the specific mechanisms and neuroanatomical areas that underlie these cognitive improvements.

Disclosures: G. Betts: None.

Poster

PSTR106. Neural Mechanisms: Choice

Location: WCC Halls A-C

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Topic: H.03. Decision Making

Support: Michael Smith Health Research BC Trainee Award (RT-2020-0564)
NSERC (RGPIN-2017-05006)
CIHR (PJT-162312)

Title: Computational modeling reveals the use of differing decision-making strategies that explain task performance on a cognitively effortful attention task in rats.

Authors: *C. HALES[1], C. WINSTANLEY[2];
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Decision making often involves determining whether the cognitive effort required is worth it for the desired outcome. Motivational deficits and inappropriate use of attentional resources during decision making are common features in most psychiatric illnesses. The rat Cognitive Effort Task (rCET), a rodent model of cognitive rather than physical effort, is a cognitively demanding attentional task that requires animals to choose between an easy or hard visuospatial discrimination, with a correct hard choice more highly rewarded. Within a population of rats, like in humans, there is stable individual variation in choice behavior. In previously published analyses, animals were divided into two groups - workers and slackers - based on their mean preference for the more cognitively demanding, but more lucrative, option. Although we have found that workers and slackers differ in their response to amphetamine and other drugs, the rationale for using this criterion for grouping was not robust. By collating experimental data from multiple cohorts of male and female rats performing the rCET, we have used the drift diffusion model to identify the decision-making processes that underlie this variation in choice behavior. Workers and slackers differ in the model parameters relating to rates of evidence accumulation, bias in decision starting point, and also the distance between the thresholds for choosing one option over another. Furthermore, when entering both model parameters and behavioral measurements into a k-means cluster analysis, we verified that workers and slackers are statistically different groups, but also found distinct profiles within these groups. These subgroups correspond to differing performance on the attentional part of the task, which is linked to distinct decision-making profiles on the choice part. Reanalysis of previous pharmacology data using this model-based framework may provide important insight into the mechanisms through which different neurotransmitter systems impact cognitively effortful attention and decision-making processes, with relevance to multiple psychiatric disorders.

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Poster

PSTR106. Neural Mechanisms: Choice

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Topic: H.03. Decision Making

Support: National Key R&D Program of China (No. 2021YFA1101804)
National Science and Technology Innovation 2030 Major Program (No. 2021ZD0203700 / 2021ZD0203704)

Title: Dynamic balance and asymmetry in the population activity between direct- and indirect-pathway striatal projection neurons during decision-making

Authors: *S. TANG[1,2,3], L. CUI[1,2,3], J. PAN[1], N. XU[1,2,3];
[1]Inst. of neuroscience, CAS, Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China; [3]Shanghai Ctr. for Brain Sci. and Brain-Inspired Intelligence Technol., Shanghai, China

Abstract: The direct and indirect pathway striatal projection neurons (dSPNs and iSPNs) play essential roles in movement control and decision-making. While it is known that dSPNs and iSPNs exert opposing effects on motor control and their imbalance is associated with pathological conditions, the mechanism for coordination between the two subtypes of SPNs for eliciting proper actions during decision-making remains elusive. Here, we employed deep-brain two-photon imaging to investigate single-neuron and population coding of task information in both dSPNs and iSPNs in the posterior dorsal striatum (pDS) during an auditory-guided decision-making task. Our findings show that both dSPNs and iSPNs display within-subtype heterogeneity at the single-neuron level, with distinct subpopulations in both subtypes representing contraversive and ipsiversive action choices. Importantly, while dSPNs and iSPNs exhibited overall balanced responses, single-cell resolution analysis revealed a greater contralateral dominance and inter-neuronal synchronization in dSPNs compared to iSPNs during task performance, indicating a dynamic shift in balance likely enabling the selection of contraversive actions. These results propose a population-based mechanism for coordinating the dSPN and iSPN ensembles in action selection during decision-making.

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Poster

PSTR106. Neural Mechanisms: Choice

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Topic: H.03. Decision Making

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Title: Manipulating choice engrams in the premotor cortex during a multiple-choice delayed-response task

Authors: *B. SERRANO PORCAR[1,2], R. MARIN[1], C. SINDREU[1,2], J. DALMAU[3,4,5,6,2], A. COMPTE[1], T. J. RYAN[7,8,9,10,11], J. DE LA ROCHA[1];
[1]Brain Circuits and Behavior Lab., Inst. d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [2]Univ. de Barcelona, Barcelona, Spain; [3]Pathogenesis of autoimmune neuronal disorders, Inst. d’Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [4]Neurol. Dept., Inst. of Neuroscience, Hosp. Clínic de Barcelona, Barcelona, Spain; [5]Dept. of Neurol., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; [6]Catalan Inst. for Res. and Advanced Studies (ICREA), Barcelona, Spain; [7]Sch. of Biochem. and Immunology, Trinity Col. Dublin, Dublin, Ireland; [8]Max Planck Inst. for Human Develop., Berlin, Germany; [9]Trinity Col. Inst. for Neuroscience, Trinity Col. Dublin, Dublin, Ireland; [10]Florey Inst. of Neurosci. and

Mental Health, Melbourne Brain Centre, Univ. of Melbourne, Melbourne, Australia; [11]Child & Brain Develop. Program, Canadian Inst. for Advanced Res. (CIFAR), Toronto, ON, Canada

Abstract: During perceptual decision-making sensory inputs recruit neural ensembles representing specific choices that, through mutual inhibition, compete dynamically to control motor output. These choice-specific neural ensembles have been found in multiple brain areas (e.g. parietal and premotor cortices, basal ganglia, etc). Photo-inhibition of some of these areas can severely impact behavior but, except when inhibiting unilaterally in tasks with a Left-Right symmetry, these manipulations do not bias behavior with respect to a specific choice and hence cannot inform about the detailed circuit interactions during choice selection.
Aiming to label and manipulate ‘’choice engrams’’, we developed a multiple-choice delayed-response task (nDRT) where mice viewed a brief stimulus on a touchscreen presented at one of three possible locations (Left, Centre, Right), retained its position during a short mnemonic delay (~1s), and responded by poking at the remembered position. We used a c-fos-driven tagging method (TRAP2 system) together with a viral injection of a Cre-conditional reporter (AAV-EF1α-DIO-ChR2-eYFP) for the permanent expression of channelrhodopsin in anterior lateral motor cortex (ALM) neurons. To TRAP neurons specifically encoding one of the choices, we ran a labeling session with only the central stimulus such that mice made, almost exclusively, the corresponding central choice (n=10 mice). After labeling, mice resumed the normal nDRT task with photostimulation at 5 or 20 Hz in random trials (20%).
Photoactivation impacted behavior in a choice-specific manner but, contrary to our prediction, it did not bias choices towards the center. Instead, stimulation at 5Hz, but not at 20 Hz, decreased choice accuracy only in central-stimulus trials (66% vs 57%, $p<0.01$). Moreover, 20Hz stimulation decreased the fraction of response omissions also only for center-stimulus trials. These results suggest that activation of ALM ensembles can either disrupt or increase the attention towards a specific choice, depending on the stimulation frequency, but it is ineffective in introducing a systematic choice bias. This interpretation does not support a role of ALM ensembles in choice selection via competitive interactions but on the modulation and control of choice execution.

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Poster

PSTR106. Neural Mechanisms: Choice

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Topic: H.03. Decision Making

Support: DANDRITE-R248-2016-2518 from Lundbeck Foundation

Title: Orthogonal dynamics promote choice history updating and integration in the anterior cingulate cortex

Authors: *T. WOO[1], A. BARTA[2], A. G. LIBBY[3], T. BUSCHMAN[4], D. KVITSIANI[5]; [1]Aarhus Univ., Aarhus, Denmark; [2]Aarhus Univ., Arhus, Denmark; [3]Princeton Univ., [4]Princeton, Princeton Univ., Princeton, NJ; [5]Aarhus Univ. / DANDRITE, Aarhus Univ. / DANDRITE, Aarhus C, Denmark

Abstract: We often need to rely on various types of information to make optimal decisions. Nonetheless, the mere act of preserving and segregating these pieces of information falls short of sufficiency. This inadequacy arises from the evolving nature of this information. Consider a situation wherein one is engaged in a sequence of actions, such as executing a dance routine. In such a scenario, each subsequent action is inherently contingent on multiple actions that have preceded it. Merely recollecting previous immediate actions is insufficient to guide future decisions. Similar to dance routine in many sequential decision-making tasks, animals need to update their current position within a sequence and remember multiple past sequence elements to form correct decisions. For example, in a two-alternative choice task if animals have to perform "left-left-right," sequence in order to obtain rewards they must retain information about their position within the sequence, such as what was the past immediate choice, but also keep in memory what were the past two choices they made.
The focus of our study was on addressing the fundamental question of how the brain integrates and updates past sequence elements to generate accurate decisions. To answer this question, we trained mice to perform three element action sequence and recorded neuronal activities from the anterior cingulate cortex (ACC).
By analyzing the population activity of ACC, we found that there was an evolving representation of the upcoming choices (UC) and choice history consistent with task demands. Further analyses showed that the evolving representations supported the interaction between UC and choice history. We identified two major dynamics at the population level termed choice history update and choice history integration. First, we observed the representations of choice history and upcoming choices in ACC population activity using Support Vector Machine. Orthogonality between choice history significantly reduced when the corresponding choice history was updated. For instance, when UC was updated to be choice one trial back (CH1), the orthogonality between UC and CH1 significantly reduced. Second, orthogonality significantly reduced when choice history was integrated to produce UC. We found that CH1 and choice two trials back (CH2) were entangled to compute UC. On the other hand, orthogonality was maintained between decision-unrelated choice events such that UC was not updated as CH2. These interacting dynamics were found to be significantly correlated with the behavior of the animals.

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Poster

PSTR106. Neural Mechanisms: Choice

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Topic: H.03. Decision Making

Support: ERC Grant 210240

Title: Identifying a shared source of age-related decline in working memory and decision-making

Authors: *J. S. DUFFY[1], H. MCDERMOTT[2], R. WHELAN[1], R. G. O'CONNELL[1], P. R. MURPHY[3];
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Abstract: As population ageing continues to surge globally, a major imperative exists to identify mechanismsof cognitive decline associated with aging. Working memory (WM) and decision-making (DM) arefundamental building blocks of cognition that deteriorate with age. While these processes aretypically studied in isolation, recent computational and empirical studies indicate that a commonneural circuit configuration is capable of both maintaining (for WM) and integrating (for DM)information over time through shared attractor dynamics, and that this circuit is subject to sharedsources of noise and bias that shape both WM and DM behaviour. The present study leveraged thisemerging, consolidative framework for understanding WM and DM to interrogate sources of age-related decline in both functions. Young and older adults (N=33 in each group) completedpsychophysical tasks designed to parse sources of shared and unique variance in WM and DMbehaviour while high-density scalp EEG was recorded. Results from both modalities, informed byanalyses of noise and bias in WM and DM reports and decoding of task variables from EEG signals,converged to suggest a leading locus of age-related dysfunction - degraded sensory encoding - thatgives rise to a specific pattern of decline across both domains. These findings provide fundamentalinsights into the neural basis of these functions and their susceptibility to the deleterious effects ofaging. More generally, we hope that the integrative approach to understanding WM and DMdeveloped here will be of merit for pinpointing loci of dysfunction in mental disorders characterisedby deficits in both functions.

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Poster

PSTR107. Animal Behavior and Social Cognition II

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Program #/Poster #: PSTR107.01/PP14

Topic: H.06. Social Cognition

Support: NIMH R21 MH126072
SFARI 875855

Title: Automatic markerless detection and analysis of head gaze behaviors of freely moving marmosets in three-dimensional space

Authors: *F. XING[1], A. G. SHEFFIELD[2], M. P. JADI[3], S. W. CHANG[4], A. NANDY[5]; [2]Neuroscience, Psychiatry, [3]Psychiatry, [4]Dept. of Psychology, [5]Neurosci., [1]Yale Univ., New Haven, CT

Abstract: Social communication relies on the ability to perceive and interpret the direction of others' attention, which is commonly conveyed through head orientation and gaze direction in both humans and non-human primates. However, traditional social gaze experiments often involve head-fixed non-human primate subjects, which limit their behavioral repertoire. The emergence of computational ethology offers a means to explore the richness and variability of naturalistic behaviors. In this study, we employed multiple cameras to record pairs of freely moving common marmosets (*Callithrix jacchus*) interacting within transparent arenas. To accurately track the facial features of multiple marmosets, we adapted computer vision tools using deep learning networks. By employing triangulation algorithms, the detected facial features were utilized to reconstruct facial frames in three-dimensional space, overcoming occlusion challenges. A cone, oriented perpendicular to the facial frame, was modeled as a representation of the head gaze. Gaze behavior epochs were identified by examining the relative dynamic positions of the cones, including partner gaze (one animal looking at the other's face) and joint gaze (both animals looking at the same spatial location). Through a comparative analysis of familiar and unfamiliar marmoset pairs, we observed a significantly higher likelihood of unfamiliar marmosets transitioning from partner gaze to joint gaze during the early phase of their interactions. This finding suggests the enhancement of gaze following among unfamiliar dyadic pairs and highlights the potential of this fully automated system for enhancing our understanding of social gaze behaviors.

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Poster

PSTR107. Animal Behavior and Social Cognition II

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Topic: H.06. Social Cognition

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NSF GRFP Grant DGE-2139841

Title: A Novel Automated Cooperative Pulling Paradigm for Studying Cooperative Interactions in Marmosets

Authors: *O. MEISNER[1], W. SHI[2], A. NAIR[3], N. HUDSON[1], N. FAGAN[3], F. XING[1], M. P. JADI[4], A. S. NANDY[1], S. W. CHANG[3];
[1]Dept. of Neurosci., [2]Wu Tsai Inst., [3]Dept. of Psychology, [4]Dept. of Psychiatry, Yale Univ., New Haven, CT

Abstract: Cooperative behaviors play a fundamental role in the social dynamics of many species and studying them provides insights into the evolutionary origins of prosociality and the complexities of social interactions. This study investigates cooperative learning, cooperative behavior strategies, and the influence of social factors on cooperation dynamics in marmosets (*Callithrix jacchus*), a highly prosocial non-human primate species. To investigate cooperation in marmosets, we developed an automated version of the cooperative pulling paradigm, a task widely employed in animal behavior research, which requires marmosets to temporally coordinate lever pulls to cooperate and earn reward. We analyzed their learning progression and observed consistent improvements in cooperation success rates, reward earned, pulling efficiency, and inter-animal pull timing as the marmosets became proficient in the task. To ascertain that the marmosets understood the cooperation requirements, we included no-vision and non-social coordination control conditions. We found that marmosets' performance declined when they could not see one another and when they were coordinating with an automated lever rather than a conspecific, suggesting that successful cooperation in this task depends upon using social information. Employing video-based automated behavioral tracking, we utilized head orientation as a measure of gaze direction. We found that marmosets exhibited increased gaze towards their partners as they learned to cooperate and increased gaze towards one another during the cooperation condition compared to the control conditions and the non-cooperative pulling condition. Importantly, we investigated the impact of social factors on marmosets' cooperative behaviors. We analyzed the patterns of cooperation within different dyadic pairings and found that sex, dominance, and familiarity modulate marmosets' cooperative behavior dynamics. Our study reveals that marmosets learn and engage in an automated cooperative pulling paradigm, and that this behavior is facilitated by social attention and modulated by social relationships. This research enhances our understanding of marmosets' cooperative abilities and reveals influences of social information and social relationships on their cooperative behavior.

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Poster

PSTR107. Animal Behavior and Social Cognition II

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NSF DGE2139841 to O.C.M.

Title: Exploring Behavioral Dynamics in Cooperative Interactions Among Marmoset Dyads

Authors: *W. SHI[1], O. C. MEISNER[2], A. NAIR[2], N. V. HUDSON[3], N. A. FAGAN[3], F. XING[2], M. P. JADI[4], A. S. NANDY[2], S. W. CHANG[2];
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Abstract: Social interactions are complex and dynamic, requiring effective communication, outcome evaluation, and adjustment for future interactions. Non-human primates utilize social gaze as a vital means to gather social information during interactions. To explore the significance of social gaze in cooperative interactions, we studied dyadic cooperative interactions in common marmosets (*Callithrix jacchus*), using a cooperative lever-pulling task in a naturalistic setting.In this task, the marmosets were placed in separate transparent boxes, each with access to a lever and a juice tube. To obtain the juice reward, the animals were required to pull the levers simultaneously in a cooperative manner. Throughout the task, we recorded their behaviors using multiple synchronized cameras. By employing a deep convolutional neural network, DeepLabCut, we tracked and analyzed specific facial parts, including the eyes, ear tufts, forehead, and mouth. This analysis allowed us to define the animals' head gaze direction and examine the dynamics of their gaze behaviors. We quantified the instances both when the marmosets engaged in looking at one another ('social gaze') and when they focused their attention on their own juice tube ('reward gaze').With training, all three pairs of marmosets tested exhibited an increased frequency of social gaze, indicating their potential use of social information to successfully complete the cooperation task. Furthermore, we utilized a Dynamic Bayesian Network (DBN) model to investigate the behavioral dynamics encompassing gazes and lever-pulling behaviors. By quantifying the causal relationships between these factors, we discovered an augmented causal influence from social gaze to pulling over time. This result suggests that the marmosets gradually began utilizing social information to guide their cooperative pulling actions as they learned to work together. Interestingly, our analysis of the DBN models also demonstrated distinct behavioral dynamics among the different pairs of marmosets, implying that each pair may have employed unique strategies to achieve cooperation. By using advanced tracking algorithms and analytical models, these findings collectively shed light on the complex nature of social interactions among non-human primates and emphasize the role of social gaze in facilitating successful cooperative behaviors.

Disclosures: W. Shi: None. **O.C. Meisner:** None. **A. Nair:** None. **N.V. Hudson:** None. **N.A. Fagan:** None. **F. Xing:** None. **M.P. Jadi:** None. **A.S. Nandy:** None. **S.W. Chang:** None.

Poster

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Program #/Poster #: PSTR107.04/PP17

Topic: H.06. Social Cognition

Support: The Pew Innovation Fund Grant #34503

Title: Unraveling Neural Mechanisms of Insular Cortex in Empathic Decision-Making

Authors: *B. CARRASCO[1], M. A. GARCÍA PÉREZ[1], M. CONTRERAS[3], J. VALDES[2]; [1]Neurociencias, Univ. de Chile, Santiago., Chile; [2]Univ. de Chile, Santiago, Chile; [3]Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: The anterior insular cortex is a region implicated in interoceptive processing, and it plays a critical role in facilitating prosocial behaviors. Previous fMRI studies in humans have demonstrated that activity in the insular cortex is modulated in response to others experiencing pain. Additionally, it has been associated with encoding retrospective valence to guide optimal decision-making in response to pleasant and unpleasant experiences. In this study, we propose the hypothesis that the insular cortex may encode empathic decisions. To investigate this hypothesis, we conducted in vivo high-density electrophysiological recordings in rats during a novel operant conditioning task, wherein the rats could choose whether or not to inflict distress upon a conspecific in exchange for a reward. Our findings revealed clusters of neurons in the anterior insular cortex that selectively encoded specific aspects of operant behavior. Furthermore, subsets of these neurons exhibited selective modulation when the rats made decisions to cause distress or refrain from doing so to their conspecific. Gaining insights into the underlying mechanisms involved in decision-making associated with prosocial behaviors is of utmost importance for the development of future interventions targeting neuropsychiatric pathologies characterized by altered emotional perception, impaired empathy, or psychopathic-like behaviors.

Disclosures: B. Carrasco: None. **M.A. García Pérez:** None. **M. Contreras:** None. **J. Valdes:** None.

Poster

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Topic: H.06. Social Cognition

Support: Pew Innovation Fund, USA
Proyecto ACE210007 BNI

Title: Exploring Psychopathy through a Rodent Social Paradigm

Authors: *M. A. GARCÍA PÉREZ[1], B. CARRASCO[1], M. CONTRERAS[2], J. L. VALDÉS[3]; [1]Neurosci., Univ. of Chile, Santiago, Chile; [2]Univ. of Arizona, Tucson, AZ; [3]Univ. de Chile, Santiago, Chile

Abstract: Psychopathy is a personality disorder primarily characterized by a lack of empathy and violent antisocial behavior, which often inflicts significant emotional and psychological harm on its victims. Currently, the absence of an animal model to effectively address this personality disorder poses a significant obstacle in investigating potential treatments. Here, we utilized a unique operant conditioning rodent model of empathy to characterize a social paradigm that investigates the propensity to harm others while seeking personal gain. By considering factors such as familiarity, strain, and food availability, this paradigm offers valuable insights into this predisposition. During the initial phase of the task, the operant rat must establish a preference lever to acquire a reward (a drop of water with 20% sucrose). Subsequently, the operant rats face a choice between obtaining a reward by pressing the preferred lever, which comes at the expense of causing harm to the neighboring rat (either a Cagemate or Stranger) or opting to switch their preference and obtain the reward without causing harm to others.
Our findings revealed that, irrespective of whether the neighboring rat was a Cagemate or a Stranger, the operant rats consistently opted to switch their preference when it would result in causing harm to a conspecific. Interestingly, in the rat population sessions, we were able to identify and differentiate three distinct profiles: Switchers, Non-switchers, and Variable behavior. When examining the subjects' behavior, we observed that the animals who switched their preference, referred to as "Empaths," displayed a greater degree of empathy towards strangers, particularly when they were not food restricted. In contrast, the Non-switchers, whom we referred to as "Psychopaths," exhibited a consistent preference for causing harm to other rats, regardless of factors such as familiarity, strain, and food availability. This observation suggests that Non-switchers, unlike Switchers, lack of selectivity and inflict harm indiscriminately.

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Poster

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Title: Behavioral adjustment in response to others' internal state in common marmosets: AI based quantification using neural networks that predict the internal state solely from actions.

Authors: *W. LU[1], T. KANEKO[1,2], J. MATSUMOTO[3,4], X. ZHAO[1], L. UENO[1], T. OISHI[1], K.-I. INOUE[1], M. TAKADA[1];
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Abstract: In social life of primates, it's crucial to adjust one's own behavior depending on others' internal state, such as their emotions, intentions, and other physiological demands. These events may not be readily observable but can be noticed by watching over others. Several human neuroimaging studies have shown a neural substrate that is involved in such a cognitive function. However, only a few studies have addressed this issue in nonhuman primates since the nonverbal behavioral paradigm is so limited that the detailed underlying mechanism cannot be investigated. Here we aimed to overcome this issue by introducing a state-of-the-art artificial intelligence (AI) system to quantify marmosets' actions and internal states. Using a markerless motion capture system consisting of multiple deep neural networks that quantify actions by common marmosets, and Long Short-Term Memory (LSTM), a type of neural network for temporal data analysis, we examined whether actions by one marmoset (i.e., subject) might reflect the difference in the internal state of the other (i.e., partner). We devised a food competition experiment in which two adult marmosets competed for a single reward. Before each trial, we controlled the partner's internal state to be either hungry or full. At the beginning of a trial, a valuable food ball was given to the subject, and the partner might try to take away or beg for the food from the subject who needed to pay attention to the partner's behavior. The LSTM could successfully predict the internal state of the partner marmoset solely from his/her three-dimensional posture time-course data. Furthermore, the partner's internal state could also be accurately decoded by the LSTM based on the subject's actions, indicating that the subject indeed adjusted his/her own behavior in response to the partner's internal state. We further demonstrated that the subject's reaction towards the same action by the partner was changed according to the partner's internal state. The present results have revealed the cognitive complexity of marmosets in the social context. This implies that marmosets flexibly adjust their behaviors in response to the others' internal state. We plan to combine our behavioral paradigm with pharmacological and genetic manipulations to explore a neural substrate that may be involved in flexible behavioral adjustment.

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Poster

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Topic: H.06. Social Cognition

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Title: Juvenile peer-social interactions may shape adult aggression and dominance

Authors: *A. SOLIS[1,2], H. YUEH[2], M. CHAU[2], J. VEENSTRA-VANDERWEELE[2], K. C. O'REILLY[2];
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Abstract: Social function requires sophisticated communication, emotional modulation, and behavioral adaptation skills needed to negotiate complex interactions. Social competence is therefore essential for the development and maintenance of social support groups and is a protective factor for good mental health. In children, peer interactions may help develop the social and cognitive skills required for later social function, but the role of peer interactions in shaping adult social competence has only been superficially investigated. We hypothesized that juvenile peer interactions modulate development of neural circuits that allow mice to regulate behaviors during later social interactions. To investigate the role of peer interactions on later social function, mice were housed in groups of 3-4 littermates (peer-housed, PH), or alone with their dam (peer-deprived, PD) from postnatal days 21 (P21, the typical time for weaning) to P35. Our data suggests that peer-deprivation during this developmental period can lead to aggression during juvenile peer encounters (latency to aggress = 488 ± 70s), which was not observed in PH mice (latency to aggress = 600 ± 0s). Furthermore, adult males that were peer-deprived during the juvenile period show increased aggression in the Resident Intruder assay (PD= 26.2 ± 5.7 aggressive events; PH= 11.4 ± 2.32 aggressive events) and dominance in the Tube Test (PD= 74 ± 11% wins; PH= 40 ± 6% wins) toward novel conspecifics, as well as unusual aggression toward intruder females (PD= 9.3 ± 4.8 % time spent in aggression; PH 0.1 ± 0.1 % time spent in aggression). We also replicated studies showing that the ventral medial hypothalamus (VMH) controls aggression [Lin et. al., *Nature* 2011] using mice expressing Cre under the control of steroidogenic factor 1 (SF1-Cre). Aggression was assessed at least three weeks following injection of AAV2-hSyn-DIO-HM4Di (inhibitory DREADD) into the VMH of adult male mice. Administration of clozapine-N-oxide (CNO) reduced the percent of time SF1-Cre+ mice spent aggressing a novel intruder (0.2 ± 0.1 % time) compared to SF1-Cre- mice (1.5 ± 0.5 % time). Future studies will utilize circuit manipulations of the developing VMH to uncouple neuronal activity from typical social interactions during the juvenile period.

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Poster

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Topic: H.06. Social Cognition

Support: NIH Grant 5R00MH106744-05

Title: Hierarchy-dependent changes in social behavior during sickness

Authors: *H. LANOVOI[1], R. OYAMA[1], J. SALAZAR[1], D. AGYEMANG[1], Y. HOLGUIN[1], J. S. RICEBERG[2], I. CARCEA[1];
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Abstract: Social behaviors play profound roles in animal survival. Pathogen-infected members of a group adapt their social decisions to prevent the spread of infection while also seeking familiar support. To model sickness we treated mice with LPS (0.5mg/kg) and then assessed social preference for novel or cagemate mice at 2 hours after injection. We find that unlike control, saline injected mice, LPS treated mice have a mixed preference to investigate either novel or cagemate conspecifics (choice index (Cagemate-Novel)/(Cagemate+Novel) for 'Saline':-0.2982, $p<0.0001$, and 'LPS':0.001049, $p=0.9934$). We reasoned that social hierarchy might explain the mixed preference observed in mice during acute sickness. To assess the role of social hierarchy in social preference during sickness we used the tube test. We find that unlike healthy dominant mice, sick dominant mice investigate cagemates more than novel conspecifics ('Saline-dominant': -0.2852, $p=0.0029$, 'LPS-dominant': 0.5329, $p=0.0048$). We then investigated putative brain mechanisms that might underlie the changes we observed in social preference during sickness. We focused on the central amygdala (CeA) as this structure is c-fos responsive to sickness and part of a brain network involved in social approach and avoidance. A subset of cells in CeA express the receptor for the neuropeptide oxytocin (OTR+). We next assessed if CeA-OTR+ cells respond to sickness by measuring c-fos expression 2 hours after injection of either LPS or saline. We find an increase in c-fos+ OTR+ cells in the CeA of LPS-treated mice ('Saline': 0.41%, 'LPS': 16.64%, $p=0.0034$). Preliminary photometry recordings during the social preference task indicate that CeA-OTR+ neuron activity encodes the orientation and proximity to conspecifics. The effect of hierarchy and treatment on CeA-OTR+ activity mirrors behavioral outcomes. We hypothesized that LPS impacts the activity of CeA-OTR+ cells through changes in ascending visceral inputs or alternatively via local neuroinflammation. We used monosynaptic retrograde rabies tracing to determine if CeA-OTR+ neurons receive synaptic inputs from viscerally responsive brain structures. We find CeA-OTR+ projecting cell populations in two LPS-responsive structures. To determine if CeA-OTR+ cells can directly respond to local neuroinflammation, we assessed the expression of prostaglandin receptors using RNAscope. We find that CeA-OTR+ cells express prostaglandin receptor EP2. Future experiments will determine by which mechanisms sickness activates CeA-OTR+ neurons, and whether this activation impacts hierarchy- and treatment-dependent social preference behavior.

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THE HORI SCIENCE AND ARTS FOUNDATION
KAKENHI22H04931

Title: Action in unison as real-time social interactions in macaques

Authors: *S. TOMATSU, M. ISODA;
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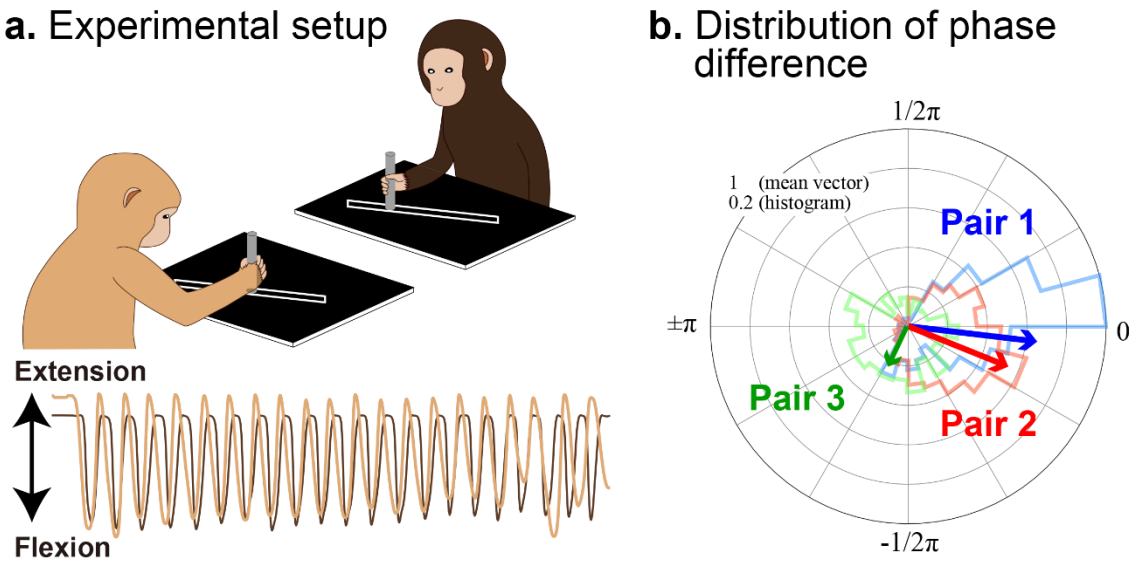
Abstract: Movement synchronization between individuals is ubiquitous in humans and has been implicated in reinforcing their cohesion. How might such inter-individual motor entrainment be controlled by the social brain? The answer remains elusive, owing largely to the lack of suitable animal models in which direct neural recordings are available. Here we show that Japanese monkeys (*Macaca fuscata*) exhibit social motor entrainment without prompting by the experimenters. Two monkeys sat face-to-face and performed repetitive arm movements for horizontal bar-sliding with their own preferred rhythms (panel **a**). There was no extra reward for the occurrence of any kind of synchronization between their movements; the only requirement was to observe each other's bar/arm motion. We found that the movements between two monkeys were phase coherent. The nature of motor entrainment was specific to animal pairs (panel **b**), consistent across days, dependent on visual inputs, and affected by social hierarchy. Notably, the entrainment was diminished when the monkeys performed the movements during observing pre-recorded movies of another monkey making the same movements or observing pre-recorded bar motion alone. Furthermore, the causality analysis, as indexed by transfer entropy, indicated that the high ranked monkey was more likely to tune in to the other's movement. These findings demonstrate that motor entrainment is facilitated by real-time social exchanges, providing a novel behavioral platform to study the neural basis of potentially evolutionarily conserved mechanisms that support group cohesion.



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Poster

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Topic: H.06. Social Cognition

Title: The role of perineuronal nets in the medial prefrontal cortex on social dominance hierarchies in rats

Authors: ***R. M. BURCH**, J. R. HINMAN;
Psychology, Univ. of Illinois, Champaign, Urbana, IL

Abstract: Rodents are highly social animals living in colonies of several dozen to hundreds of individuals. Rats utilize social dominance hierarchies to navigate these complex social networks, dictate the dispersion of resources, such as food and territory, and reduce conflict within a group. Changes in the medial prefrontal cortex (mPFC) significantly alter behaviors critical to a stable hierarchy, with plasticity at medial dorsal thalamic synapses on mPFC neurons playing a critical role in an individual's hierarchy position. Additionally, excitation or inhibition of mPFC neurons can shift an animal up or down the hierarchy respectively. In the mPFC of rats, the presence of perineuronal nets (PNNs) increases through adolescence into adulthood, maintaining connections that are critical to developing behaviors, such as social behaviors. PNNs, an extracellular protein structure, stabilize synapses made onto parvalbumin (PV) interneurons, minimizing alterations of existing connections. The ablation of PNNs via chondroitinase ABC (Ch-ABC) can return a region to a juvenile-like state of plasticity, including decreased PV interneuron firing rates.We investigated the role PNNs in mPFC play in the maintenance of stable social hierarchies. Given

the decrease in PV interneuron firing rates following PNN ablation, we hypothesized that would lead to increased activation of principal cells measured by the upregulation of c-fos, an immediate early gene used as a neuronal activity marker. We ablated PNNs in mPFC via intracranial injection of Ch-ABC in male and female rats and 1 or 3 weeks later tested the animals in a palatable liquid competition paradigm prior to euthanasia and tissue processing for c-fos, PNNs and PV+ cells. We hypothesized that the loss of PNNs would result in increased c-fos expression in the region of the ablation and that increased activity of principal cells would alter social behavior and increase variability in established social hierarchies. To test this idea, we ablated PNNs in mPFC of same sex groups of four adult male or female Long-Evans rats with established, stable social hierarchies. Our results demonstrate that the ablation of PNNs does not significantly influence the stability of social hierarchies in either male or female rats. We additionally considered changes in a host of behaviors that could influence the stability of hierarchies such as social preference, social recognition, anhedonia, and locomotor activity, without detecting a role of PNNs in any behavior. Further exploration of the mPFC's role in social hierarchy maintenance and formation could help elucidate the neural mechanisms that contribute to these complex social structures.

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Poster

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NRF-2019M3E5D2A01058328

Title: A blending of innovators and imitators for the optimization of multi-agent behaviors

Authors: *S. BAEK[1,2], S.-B. PAIK[3];
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Abstract: Innovators, exhibiting novel behaviors not observed previously in the population, are observed in both human and nonhuman animal populations (Fisher, 1949; Reader, 2003). It has been hypothesized that they play a major role in the evolution of population behavior by exploring new niches, permitting the diversification of behaviors and traits, and enhancing fitness and adaptability (Tebbich, 2016). Despite these predictions that the role of innovators is crucial in a group, no instances have been reported in which innovators become a dominant group in the population. Instead, imitators, who copy the actions or traits of others, are often observed to be dominant (Reader, 2016). A recent model study suggested that random copying of others can improve the fitness of a population and accelerate the evolution of traits to optimal

levels in a multi-agent condition (Kang, 2022). This raises questions about the mechanisms and conditions under which innovators can improve the efficiency of a population. Using a computational approach with a multi-agent system, here we show that a certain proportion of both imitators and innovators is required to induce the evolution of population traits. To validate this scenario, a model of multi-agent survival was designed. Each agent in this model has a single trait parameter that determines its shape. The agent's shape modulates the amount of energy it collects and consumes efficiently. We found that a population consisting solely of innovators, whose traits evolve randomly and differ significantly from those of others, cannot increase the survival time of individual agents, as the traits of individuals could not trend toward an optimal value for survival. Similarly, a population consisting solely of imitators who randomly copy the traits of others also cannot increase the survival time of individual agents effectively. Notably, however, when both innovators and imitators were implemented together in the population, the trait converged rapidly to an optimal value. In addition, in simulations in which the ratio of innovators to imitators was altered, we observed that a trait's optimal value could be reached only when the ratio of imitators exceeded a certain threshold. Overall, our results suggest that the roles of innovators and imitators are strongly correlated with each other; the innovator acts as the effect's seeder, and the imitator acts as its propagator, implying that the coexistence of innovators and imitators can be a general configuration required for the evolution of a population.

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Intramural Research Grants for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry (3-9)

Title: Involvement of the oxytocin signaling in the transmission of social stress in mice

Authors: *Y. NAKATAKE[1], H. FURUIE[1], Y. U. INOUE[2], T. INOUE[2], K. YOSHIZAWA[3], M. YAMADA[1,4];
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Abstract: Emotional contagion is a phenomenon in which emotional expression of an individual causes similar emotional state in the others who observe it. It is conserved in a variety of species, including rodents, and plays an important role in social communication with others. On the other hand, the transmission of stress with negative emotions induces long-term emotional and

physiological changes in mice. The neuropeptide oxytocin is known to facilitate emotional contagion; however, the role of the oxytocin system in the transmission of stress and subsequent stress-related changes has not been fully clarified. In the present study, we used the witnessing social defeat paradigm to examine the role of oxytocin system in the transmission of social stress and modulating stress-related behavioral changes. In the witnessing session, C57BL/6J mice (8-9 weeks, male) were placed in the home cage of aggressive ICR mice (retired, male) and exposed to attacks from the ICR. The observer C57BL/6J mice (8-9 weeks, male) witnessed socially defeated conspecifics for 10 min through a transparent partition in the same cage. First, we assessed c-Fos expression to investigate the neural activity after social stress transmission. We found that the number of c-Fos-positive cells in the anterior insular cortex (aIC) was increased only after witnessing social defeat, but not after actual experience of social defeat. Furthermore, the percentage of c-Fos-positive cells in oxytocin receptor-expressing neurons was increased in the aIC after witnessing social defeat. We next examined whether oxytocin signaling was involved in the transmission of social stress. We found that microinjection of an oxytocin receptor antagonist into the aIC suppressed freezing behavior during witnessing session and also decreased the levels of plasma corticosterone after the session. On the other hand, microinjection of oxytocin receptor antagonist did not affect freezing behavior and corticosterone levels induced by actual social defeat. In addition, we found that the optogenetic inhibition of oxytocin receptor-expressing neurons in the aIC during witnessing session prevented the subsequent reduction of social behavior and reward sensitivity. Our results suggest that oxytocin signaling in the aIC mediates the transmission of social stress and underlies subsequent behavioral changes. We are currently investigating neural projections from the aIC to identify brain regions responsible for the expression of emotional changes induced by the transmission of social stress.

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Poster

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Support: SRNSFG: Grant # - YS-19-1737.

Title: Environmental enrichment improves the behavioral and structural alterations in rats prenatally exposed to valproic acid

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Abstract: Autism spectrum disorders (ASD) represent a heterogeneous group of disorders characterized: difficulties in social interactions, issues with verbal and nonverbal communication, and repetitive behaviors. Despite many research there is no agreement about the causation of autism, and the etiopathogenetic factors of ASD are unknown. Currently, no pharmaceutical compound is approved to alleviate the core symptoms of ASD. Still, environmental enrichment remains promising for ASD. The aim of the study is to investigate effects of environmental enrichment on the behavioral and structural alterations in rats prenatally exposed to valproic acid (VPA). Female outbred white rats were mated overnight, and the morning when spermatozoa were found was designated as the first day of gestation. Females received a single intraperitoneal injection of 500 mg/kg sodium VPA on the 12.5 day after conception, and control females were injected with physiological saline at the same time. On the postnatal day 7 (PND7) half of the offspring from Control (C) and VPA treated (V) group were housed an enriched environment (EE) and the other half were rearedin standard environment (SE). Behavioural experiments startedon postnatal day (PND) 30 - 35. Sociability was evaluated in a three-chamber apparatus; Eye opening was observed from days 12 to 16. Purkinje cell loss in cerebellumwas evaluatedby the classical histological Nissl staining method. Our results showed maturational delay - later eye opening in prenatally VPA treated groups. In the sociability test V-SE group stayed more time in the empty space and their staying time in the compartment with a conspecific rat was significantly lower than in V-EE groups ($P = 0.013$) suggesting the deficits in sociability, but was lower than in the control group ($P < 0.01$). Our results showed that the total number of Purkinje cells in the V-EE group was significantly higher than in the V-SE group but was lower than in the C-SE and C-EE groups. In conclusion, the present study demonstrates that the environmental enrichment during early developmental age improves deficit in sociability in a VPA-exposed rat model of ASD and it prevents prenatal VPA-induced loss of Purkinje cells in the cerebellum. Our results bring further support to the validity of the proposed VPA animal model of autism and reinforce the importance of this model for the preclinical investigation of new therapeutic approaches. **The study was supported by funding from the SRNSFG: Grant # - YS-19-1737.**

Disclosures: L. Kruashvili: None. **N. Chkhikvishvili:** None. **M. Chighladze:** None.

Poster

PSTR107. Animal Behavior and Social Cognition II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR107.14/PP27

Topic: H.06. Social Cognition

Support: NIH Grant R01MH099660
NIH Grant R01DC015776
NIH Grant R21HD053114

Title: Structural alterations in the amygdaloid complex and impaired social incentive learning in a mouse model for a genetic variant associated with neurodevelopmental disorders

Authors: *T. HIRAMOTO[1], A. SUMIYOSHI[2,3], R. KATO[4], T. YAMAUCHI[1], G. KANG[1], B. MATSUMURA[1], L. J. STEVENS[1], R. RYOKE[3], H. NONAKA[3], A. MACHIDA[4], K. NOMOTO[4], K. MOGI[4], T. KIKUSUI[4], R. KAWASHIMA[3], N. HIROI[1];
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Abstract: Copy number variants (CNVs) are robustly associated with psychiatric disorders, their behavioral dimensions, and brain structural alterations. However, as CNVs contain many genes, the precise gene-phenotype relationship remains unclear. Although various volumetric alterations in the brains of 22q11.2 CNV carriers have been identified in humans and mouse models, it is unknown how the genes in the 22q11.2 region individually contribute to structural alterations and mental illnesses and their dimensions. Our previous studies have identified *Tbx1*, a T-box family transcription factor encoded in 22q11.2 CNV, as a driver gene for social interaction and communication, spatial and working memory, and cognitive flexibility. However, it remains unclear how *Tbx1* deficiency impacts the volumes of various brain regions and their functionally-linked behavioral dimensions. In this study, we used volumetric magnetic resonance imaging (MRI) analysis to comprehensively evaluate the volume alterations of brain regions and their associated behavioral consequences in congenic *Tbx1* HT mice. Four month-old female *Tbx1* HT mice (n=7) and their female WT littermates (n=11) were used for MRI analysis. The volumes of anterior and posterior portions of the amygdaloid complex and its surrounding cortical regions were selectively reduced in *Tbx1* HT mice. We next capitalized on a place-conditioning procedure, a classical conditioning known to rely on the amygdala. One month-old male *Tbx1* HT mice (total n=41) and their male WT littermates (total n=35) were tested for social incentive learning with or without a social partner in this task. *Tbx1* HT mice were impaired for their ability to detect the incentive value of a social partner. Our findings identify *Tbx1* as a driver gene of 22q11.2 CNV for the structural basis for a specific social dimension.

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Poster

PSTR107. Animal Behavior and Social Cognition II

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR107.15/PP28

Topic: H.06. Social Cognition

Support: Harris Research Endowment

Title: Relationship between barbering and dominance hierarchy in B6129SF2/J male mice

Authors: *K. R. REIMAN, L. M. MONSON, C. C. WRENN;
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Abstract: Mice are social animals that form dominance hierarchies. Hierarchies influence the behavior and physiology of animals, which makes them an important area of study for biomedical research. Barbering, which is the removal of an individual's fur or whiskers by a conspecific, is a mouse behavior hypothesized to be related to hierarchy position. A previous study in our laboratory using aged B6129SF2/J mice found a positive correlation between barbering severity and social dominance, counter to reports of other mouse strains. We began this longitudinal study with the primary purpose of testing whether the positive correlation would replicate in young mice. A second purpose of this study was to observe whether hierarchies change over time and whether barbering plays a role in hierarchy establishment and stability. Over a span of 8 months, we performed monthly assessments of barbering extent. These results were compared to hierarchy status derived from the tube test of social dominance. The results show that in 6 of the 9 cages that have barbering, there is a positive correlation between barbering extent and hierarchy position. We also found that the hierarchies of each cage are stable, with 7 of 10 cages having the same dominant mouse for at least 6 of 7 possible months. Our observation that barbering is related to hierarchy suggests that visual inspection of barbering extent may serve as a proxy for determining hierarchy position and thus provide a convenient a way of avoiding biased grouping of mice in laboratory studies.

Disclosures: K.R. Reiman: None. **L.M. Monson:** None. **C.C. Wrenn:** None.

Poster

PSTR107. Animal Behavior and Social Cognition II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR107.16/QQ1

Topic: H.06. Social Cognition

Support: NIH Grant R01AG071787

Title: Deciphering neuronal activation patterns underlying prosocial behavior in mice

Authors: *H. LEE, D. ALONZO, J. LU, Y. ZUO;
Univ. of California Santa Cruz, Santa Cruz, CA

Abstract: Interactions with conspecifics are an essential part of the life of social animals. Many species ranging from insects to humans exhibit a rich repertoire of prosocial behaviors, including sharing, cooperation, and other forms of caring and helping behaviors. A common theme of these behaviors is that they are other-directed actions that benefit others. Recent studies show that mice exhibit prosocial behaviors such as allogrooming toward distressed conspecifics (consolation-like behavior). To study mouse prosocial behaviors, we set up a test in which an observer mouse and a demonstrator mouse freely interact for 15 min in an open-top arena. We found that the observer makes comparable approaches and sniffs toward the demonstrator

regardless of whether the demonstrator is stressed. However, the observer exhibits more allogrooming towards the stressed demonstrator than the unstressed control. Interestingly, we observed no significant difference in prosocial behavior between cagemate and non-cagemate interactions, indicating that mice can discriminate others' emotional states and provide proper consoling behavior regardless of familiarity. Such differential response toward stressed vs unstressed demonstrators is not diminished by aging, suggesting that aged mice retain the ability to detect and evaluate the affective states of their conspecifics. Next, we used Targeted Recombination in Active Populations (TRAP) mice, in which Cre-ERT2 is driven by the c-Fos promoter, to identify brain regions involved in prosocial behavior. TRAP mice crossed with Ai14 (cre-dependent mCherry reporter mice) were injected with 4-hydroxytamoxifen to induce mCherry expression in activated neurons after the prosocial behavior test. We are currently examining brain-wide activity patterns for prosocial behavior, which allows us to find candidate brain regions to investigate.

Disclosures: H. Lee: None. **D. Alonzo:** None. **J. Lu:** None. **Y. Zuo:** None.

Poster

PSTR107. Animal Behavior and Social Cognition II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR107.17/QQ2

Topic: H.06. Social Cognition

Support: KAKENHI JP 18K10852

Title: Long-term voluntary exercise promotes empathy-like behavior through the activation of oxytocin neurons in rats

Authors: *N. KUBOTA[1,2], A. MORIOKA[2], S. AMEMIYA[2], I. KITA[2];
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Abstract: Regular exercise has been reported a significant benefit for our physical and psychological health through changes in brain activity. In sporting activities, especially team sports, the empathy skills of individuals might be important. Empathy is the recognition and internalization of feelings, states, or behavior of others, and important for the survival and maintenance of society. However, few studies experimentally examined the relationships between exercise and empathy, and the effects of regular exercise on empathic behavior. Our hypothesis is that long-term exercise promotes empathy-like behavior via facilitating neuronal activation of oxytocin (OXT), a physiological key player in empathy. To examine this hypothesis, in the present study, we performed a behavioral task of helping soaked conspecifics as an empathy-like behavior model, according to Sato et al. (2015), using male rats. Furthermore, we evaluated the activation of OXT neurons in the PVN during represented helping situation using immunohistochemistry. Helper rats were individually housed in the cage with running wheel (EX-G), or without running wheel (no-EX-G) for 4 weeks. Demonstrator rats (i.e., soaked

rats) were housed in the normal cage with 3-4 rats for 4 weeks. After that, we performed the helping task in helper and demonstrator rats for 6 consecutive days (up to 5 min/day; HELP condition). We also performed a similar task to a helper rat without a soaked rat as the control (EMPTY condition). In each condition, we measured the time to the door-opening and the time spent in the interaction zone that is the area within 5 cm from the door to estimate the motivation for empathy-like behavior. Helper rats faced a different demonstrator every experimental session to exclude confounding factor by the familiarity, which is required for the expression of empathic behavior. In the HELP condition, the time to door-opening and the time spent in the interaction zone in EX-G were decreased and increased with repeated experimental sessions. These results showed that long-term voluntary exercise can promote helping behavior. Furthermore, EX-G showed significantly higher activation of OXT neurons in the PVN during the helping situation compared to no-EX-G in the HELP condition and EX-G in the EMPTY condition. In addition, we found that the facilitating effect of helping behavior obtained in EX-G was inhibited by OXT antagonist (icv). These results suggest that long-term exercise promotes empathy-like behavior toward unfamiliar conspecifics through the activation of OXT neurons.

Disclosures: **N. Kubota:** None. **A. Morioka:** None. **S. Amemiya:** None. **I. Kita:** None.

Poster

PSTR107. Animal Behavior and Social Cognition II

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Program #/Poster #: PSTR107.18/QQ3

Topic: H.06. Social Cognition

Support: European Research Council (ERC) grant n°818521

Title: Hierarchy and Hemispheric Lateralization in Squirrel Monkey (Saimiri sciureus)

Authors: *J. ROYO[1,2], T. ORSET[1,2], P. POUGET[1,2], M. THIEBAUT DE SCHOTTEN[2,3];
[1]Inst. du Cerveau (ICM), Paris, France; [2]Brain Connectivity and Behaviour Lab., Paris, France; [3]Groupe d'Imagerie Neurofonctionnelle (GIN), Bordeaux, France

Abstract: Animal species are often organized hierarchically based on dominance rank giving privileged access to resources and reproduction. The dominant structure of social groups depends on many factors, such as animal attributes or self-organizing social dynamics. Once the hierarchy has been established, it remains relatively stable through some behaviors from dominant individuals over subordinates (punishment, threats⋯). Few studies have examined the link between dominance and brain organization with behavioral and imaging measures, especially in primates. We investigated this relationship in the squirrel monkey (Saimiri sciureus) to better understand the neurological substrates. First, pairwise social testing determined the dominance rank in 15 female animals. Then, we acquired a high-resolution, multishell diffusion-weighted dataset with an 11.7 T MRI scanner to study the differences across the animals. By compiling test results, we noticed that the hierarchy was linear within our group of animals. Moreover, we

observed a strong presence of aggressive behaviors from dominants and stress and withdrawal behaviors on the part of subordinates. Imaging analysis (fractional anisotropy) showed that the volume of the uncinate fasciculus and the superior and inferior cingulum was inversely proportional to the dominance. Thus, the more animals are dominant, the more the volume of these brain areas is reduced. These results are consistent with behavioral and imaging studies of psychopathy in humans and chimpanzees. We conclude that dominance among social groups would follow a triarchic model with disinhibition, meanness, and boldness factors which are more important in hierarchically high individuals.

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Poster

PSTR107. Animal Behavior and Social Cognition II

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Program #/Poster #: PSTR107.19/QQ4

Topic: H.06. Social Cognition

Support: Nos. NRF-2022R1A2C3008991
NRF-2021M3E5D2A01019544
NRF-2019M3E5D2A01058328

Title: Random imitation as an efficient survival strategy in multi-agent systems

Authors: *G. KIM[1], *G. KIM[2], M. KANG[3], H. LEE[3], Y. PARK[3], M. SONG[3], S.-B. PAIK[2]; [2]Brain and Cognitive Sci., [3]Bio and Brain Engin., [1]KAIST, Daejeon-City, Korea, Republic of

Abstract: Imitation, the act of copying the behaviors of others, is an essential function of humans and animals that facilitates learning and development. Conventionally, it is generally assumed that humans and animals copy more effective traits, not those chosen at random, as a payoff-biased strategy. However, it has been reported that imitation in humans and other animals often takes the form of random copying, with the possibility of imitating a suboptimal target also existing. This raises the question of whether random copying can be beneficial enough to serve as a viable behavioral strategy. Here, using a computer simulation of multi-agent survival models, we demonstrate that random copying can optimize individual agent traits, resulting in significantly increased group-level survival time across different environments. In our model, an agent's lifespan is determined by a single trait that can be changed by imitation or by random mutation. When agents were only mutated without imitation, their average lifespan did not change significantly over time. In contrast, when agents were allowed to imitate each other randomly, their average lifespan increased monotonically over time and their traits converged to the optimal trait in the given environment. Modulation of the timings and frequencies of random copying revealed that early one-shot random copying maximizes the lifespan increase of the agent group. The effect of random copying on trait optimization for survival was comparable to

or even superior to that of selective copying based on a payoff evaluation, suggesting that random copying has the potential to serve as a better survival strategy in a multi-agent system. Furthermore, we confirmed that the effect of random copying generalizes to a multi-trait model, where an agent's survival depends on multiple traits rather than a single trait. Even in a multi-trait condition, allowing agents to copy traits of other agents randomly led to a significant increase in the average fitness of the population. Notably, as the number of traits was increased, the optimization effect of random copying became more pronounced, outperforming even the ideal selective copying strategy in which agents copy the traits of the best-performing agent. Our results highlight the fact that individual-level suboptimality of random copying can promote population-level optimization, meaning that random copying can be considered an effective strategy for human and animal behaviors.

Disclosures: **G. Kim:** None. **G. Kim:** None. **M. Kang:** None. **H. Lee:** None. **Y. Park:** None. **M. Song:** None. **S. Paik:** None.

Poster

PSTR107. Animal Behavior and Social Cognition II

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Program #/Poster #: PSTR107.20/QQ5

Topic: F.01. Neuroethology

Support: 111-2313-B-002-060-MY3
108-2926-I-002-002-MY4

Title: Cholinergic Receptor Expressing Neurons in the ventral Interpeduncular Nucleus Regulate the Resolution of Experience-Dependent Social Conflicts in Zebrafish (Danio rerio)

Authors: *C.-W. FU, C.-H. HUANG, S.-K. TONG, C.-Y. CHU, M.-Y. CHOU;
Natl. Taiwan Univ., Taipei, Taiwan

Abstract: The habenula-interpeduncular nucleus (Hb-IPN) circuit regulates the resolution of social conflict in zebrafish. However, the specific location of neural interaction remain largely unknown. In the present study, we injected a neural tracer into the dorsal and ventral IPN (dIPN and vIPN) and griseum centrale (GC) and analyzed their upstream and downstream projections. The tracing data showed that the dIPN received inputs from the dorsal lateral Hb (dHbL) and projected to the GC. The vIPN received inputs from the dorsal medial Hb (dHbM) and projected to raphe. The intricate projections in the IPN may suggest its function in integrating information. The Hb-IPN circuit is the major cholinergic center in the brain. Therefore, we treated male adult zebrafish (naïve, winner, and loser fish) with nicotine for a dyadic fighting test. The results showed that nicotine treatment decreased the winning probability of naïve fish and impaired the winning and losing tendencies of winner and loser fish, respectively. We further treated dHbL and dHbM silenced fish with nicotine and conducted a dyadic fighting test to confirm nicotine affects fighting outcomes via the modulation of the Hb-IPN circuit. Nicotine impaired the

winning and losing tendencies of dHbM and dHbL silenced fish, respectively. These results suggest that cholinergic receptor-expressing neurons in the IPN reduces the winning probability and regulates the resolution of experience-dependent fights.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.01/QQ6

Topic: H.07. Long-Term Memory

Support: NIH/NIMH (R01-MH120194)
NIH/NIBIB (P41-EB018783)
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NIH/NINDS (U01-NS128612)
McDonnell Center for Systems Neuroscience
Fondazione Neurone

Title: Memory-enhancing amygdala stimulation does not affect arousal as determined from pupillometry in humans

Authors: *Z. LI[1,2,3], G. TAN[2,3], C. S. INMAN[4], S. B. HAMANN[5], J. R. MANNS[5], J. T. WILLIE[2,3,6], P. BRUNNER[2,3,6];
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Abstract: The amygdala is a brain structure located in the medial temporal lobe anterior to the hippocampus. Studies have shown that the amygdala is activated in the processing of emotions and that stimulation of the amygdala paired with the presentation of information can enhance long-term memory. However, understanding the underlying mechanisms remains elusive. One potential mechanism underlying the observed memory enhancement is thought to be related to amygdala activation caused by emotional arousal or direct stimulation that, in turn, enhances memory by modulating the plasticity in the hippocampus. Pupillometry has become a standard measure for assessing arousal state, and pupil diameter increases when people process emotionally engaging stimuli, regardless of hedonic valence. Our previous study has shown that brief basolateral amygdala electrical stimulation (BLAES) at amplitudes below subjective awareness reliably improved long-term recognition memory for images of neutral objects in

humans. In this study, we investigated the effect of BLAES on pupil diameter as a surrogate for emotional arousal. Studies have shown that declarative memory for items and scenes is linked to different oscillations in downstream memory circuits along an anterior-posterior axis of the hippocampus. We sought to explore how different visual stimuli (items, scenes) influence pupil size changes. We hypothesize that sub-threshold electrical stimulation (1mA biphasic pulses of theta-modulated gamma stimulation) of the amygdala would cause memory enhancement without pupil diameter changes. Five patients with intractable epilepsy implanted with intracranial electrodes within the amygdala participated in this study. Each patient was asked to perform a memorization task during which direct electrical stimulation of the amygdala was applied immediately following 50% of the image presentation. Throughout the experimental session, pupil diameter for each eye was measured (Tobii Pro Fusion eye-tracker, Sweden) at a rate of 120 Hz for post-hoc analysis. We applied a two-way ANOVA to determine the significance of the correlation between image stimuli showing objects and scenes and pupil size changes, and the effect of cerebral stimulation on pupil diameter changes. We found no significant relationship among image type, pupil diameter, and BLAES ($p>0.05$). The result of our negative control study confirms our hypothesis that sub-threshold BLAES does not elicit emotional arousal as measured by pupil diameter changes.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.02/QQ7

Topic: H.07. Long-Term Memory

Support: NIH Grant MH120194

Title: Direct electrical stimulation of the human amygdala enhances recognition memory for objects but not scenes

Authors: *K. L. WAHLSTROM[1], J. CAMPBELL[2], M. HOLLEARN[3], M. ADAMEK[6], J. R. SWIFT[7], L. BLANPAIN[8], T. XIE[10], P. BRUNNER[11], S. B. HAMANN[12], A. ARAIN[4], L. N. EISENMAN[13], J. R. MANNS[9], J. T. WILLIE[14], C. S. INMAN[5];
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Psychology, Atlanta, GA; [13]Washington Univ. Sch. Med., Washington Univ. Sch. Med., Saint Louis, MO; [14]Washington Univ. In St Louis, Sch. of Med., Saint Louis, MO

Abstract: Emotional events are often remembered better than neutral events — a benefit that requires the amygdala. Studies suggest the basolateral amygdala (BLA) in particular, modulates memory-consolidation processes via interactions with downstream brain regions such as the hippocampus and adjacent medial temporal lobe structures. Furthermore, direct electrical stimulation of the BLA in humans enhances declarative memory, even for non-emotional events, and this memory enhancement is marked by oscillatory interactions between the BLA, hippocampus, and perirhinal cortex. However, the BLA disproportionately projects to the anterior hippocampus and perirhinal cortex compared to the posterior hippocampus and parahippocampal cortex, regions that process non-spatial information about objects and spatial information about scenes, respectively. Nevertheless, the premise that the BLA prioritizes some kinds of memories over others has not been directly tested in humans. In the current study we tested whether brief electrical stimulation to the BLA could differentially enhance declarative memory for specific images of objects and scenes. Epilepsy patients undergoing seizure monitoring via intracranial depth electrodes viewed a series of images of neutral object and scenes, half of which were immediately followed by brief, low-amplitude electrical stimulation of the BLA. Amygdala stimulation elicited no subjective emotional response but enhanced memory for object images compared with control images when patients were given a recognition-memory test the next day. BLA stimulation had no effect on memory for scene images. The present study also leveraged the direct electrical stimulation of the BLA to dissect the effective connectivity between the amygdala and downstream brain regions, including the anterior and posterior hippocampus. Using Single Pulse Evoked Potentials (SPEP) we determined how subregions of the medial temporal lobe interact with the amygdala to favor memory for objects compared to scenes. Overall, our results suggest that the BLA initiates memory prioritization processes in the absence of emotional input by engaging other memory regions, addressing the role of the amygdala and its interactions with downstream brain regions during memory consolidation and opening a path to future therapies.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.03/QQ8

Topic: H.07. Long-Term Memory

Support: NINDS T32NS115723
NIMH R01MH120194

Title: Neurophysiological signatures of amygdala-mediated memory enhancement: insights from human intracranial recordings and stimulation

Authors: *J. M. CAMPBELL[1], K. L. WAHLSTROM[2], M. HOLLEARN[2], T. DAVIS[3], A. ARAIN[4], J. R. SWIFT[5], P. BRUNNER[5], B. SHOFTY[3], S. RAHIMPOUR[3], J. D. ROLSTON[6], J. R. MANNS[7], J. T. WILLIE[5], C. S. INMAN[2];
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Abstract: The basolateral amygdala (BLA) plays a well-documented role in prioritizing long-term memories. Recent evidence suggests that directly stimulating the BLA in humans affects theta and gamma oscillations in the medial temporal lobe (MTL)—oscillatory patterns that facilitate flexible and robust information encoding and retrieval. These evoked responses were detected during later memory retrieval, were predictive of memory-enhancing effects of stimulation, and resembled the theta-burst patterned stimulation delivered during memory encoding. However, we have a limited understanding of the temporal dynamics of these enhancement-related oscillations. To address this knowledge gap, we conducted a study using intracranial recordings from 16 human neurosurgical patients undergoing clinical monitoring for medically-refractory epilepsy. Each participant completed a visual object recognition memory task. During the task, participants were shown a series of neutral images of objects and scenes (160 images, 3 s per trial, ~5 s intertrial interval). Half of the encoding trials were followed by direct theta-burst stimulation of the BLA (bipolar, 1 s, 0.5-1 mA, 8 trains of 50 Hz). Memory performance was subsequently tested during a self-paced retrieval task ~24 hours later. Local field potentials were continuously recorded (2 kHz) during the experiments, followed by offline preprocessing, filtering into canonical frequency bands, and calculation of oscillatory power, coherence, and phase-amplitude coupling in MTL regions of interest (e.g., hippocampus). Our analysis of post-stimulation epochs revealed a rapid and persistent modulation of MTL theta and gamma oscillations relative to a pre-stimulation baseline. Furthermore, we identified specific oscillatory features (e.g., power, phase) in the pre-stimulation epochs that influenced the behavioral and neural responses to BLA stimulation. This work provides valuable insights into the neurophysiological signatures of amygdala-mediated memory enhancement. It also encourages future research on closed-loop approaches that utilize real-time recordings to optimize the therapeutic efficacy of precision neuromodulation and neural prostheses for memory.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.04/QQ9

Topic: H.07. Long-Term Memory

Support: 2022 University of Toronto-University College London Strategic Partner Funds for Project Revitalization and Scaling

Title: Magnetic resonance angiography of the medial temporal lobe: benefits of field strength and compressed sensing

Authors: M. KULKARNI[1,2], V. PEROSA[3,4], X. ZHANG[1,2], D. G. FEMMINELLA[5,6], D. HÄMMERER[6,7,3], M. F. CALLAGHAN[6], J. L. MATTHEWS[1,2], E. DUZEL[6,3], J. J. CHEN[1,8,2], *R. OLSEN[1,8,2];
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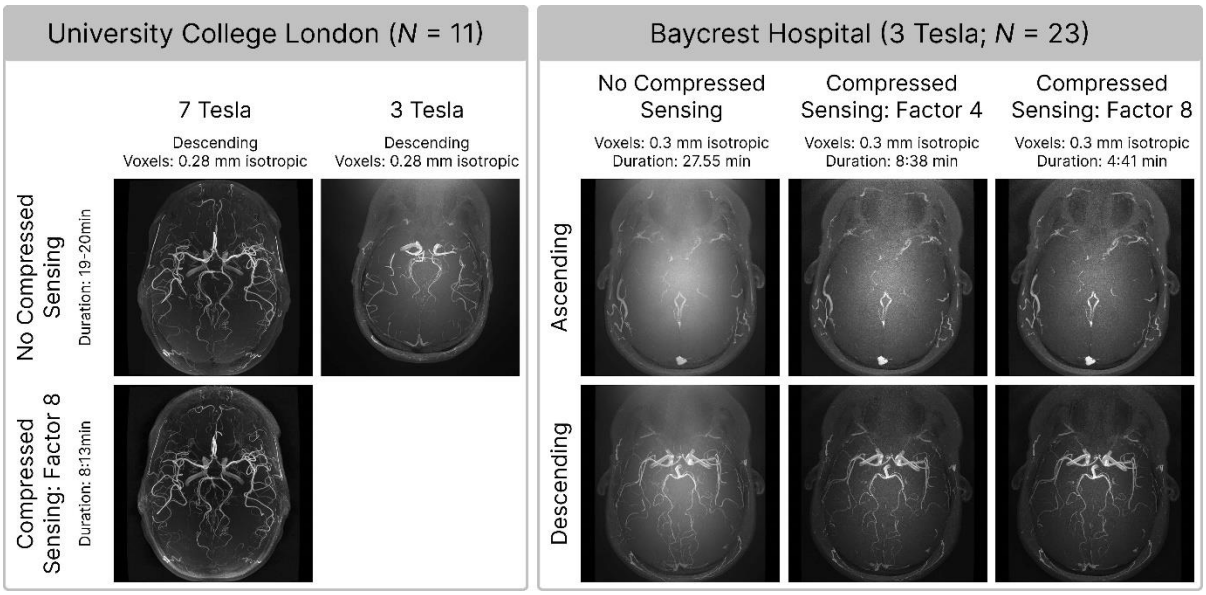
Abstract: The hippocampus and medial temporal lobe regions are crucial for episodic memory and spatial navigation. However, these structures are vulnerable to hypoxic events. The vascular supply of the hippocampus is variable and can derive from both the posterior cerebral and the anterior choroidal artery (mixed supply) or from the posterior cerebral artery only (single supply). Recent evidence suggests that mixed supply may serve as a reserve mechanism against hypoxic damage. Studying hippocampal vascularization in vivo has been a challenge due to the small size of the arteries (<0.5 mm). As a result, most previous work has exploited the greater sensitivity of 7T MRI but still resulted in long scan times (>20 mins). However, limited availability of 7T scanners restricts widespread adoption of this technique, and longer scan durations increase head motion-induced blurring limiting its use in certain special populations (e.g., children; older adults). Here, we sought to evaluate image quality and vessel depiction that could be achieved by a) using compressed sensing to reduce scan times and b) imaging at 3T to improve accessibility due to limited 7T availability. At University College London (UCL), 11 participants were scanned at 3T (20 mins) and at 7T with (8 mins) or without (19 mins) compressed sensing. A further 23 participants were scanned at 3T in Baycrest Hospital, with (8 or 4 mins) and without (28 mins) compressed sensing. Hippocampal vascular patterns were manually identified by a rater blind to field strength and protocol. In the UCL sample, vascular patterns could not be visualized at 3T. Assessment was most feasible at 7T, and without compressed sensing. However, in the Baycrest sample, compressed sensing helped with assessment of vascular patterns, possibly due to lower motion-related artifacts in these shorter scans. Finally, arteries of interest in the medial temporal lobe were better visible in scans with descending acquisition. Our findings contribute to the understanding of optimal scanning protocols for in vivo investigations of hippocampal vascularization.



Disclosures: **M. Kulkarni:** None. **V. Perosa:** None. **X. Zhang:** None. **D.G. Femminella:** None. **D. Hämmerer:** None. **M.F. Callaghan:** None. **J.L. Matthews:** None. **E. Duzel:** None. **J.J. Chen:** None. **R. Olsen:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.05/QQ10

Topic: H.08. Learning and Memory

Support: The McNair Foundation

Title: High-density electrode recordings of single neurons in the human hippocampus

Authors: *S. SHAH[1], K. A. KATLOWITZ[1], J. ADKINSON[1], R. K. MATHURA[1], N. R. PROVENZA[2], N. GIRIDHARAN[1], G. P. BANKS[1], L. LUAN[4], C. XIE[4], A. J. WATROUS[1], S. R. HEILBRONNER[3], A. M. GOLDMAN[1], A. MAHESHWARI[1], B. Y. HAYDEN[1], S. A. SHETH[1];
[2]Neurosurg., [3]Neurosci., [1]Baylor Col. of Med., Houston, TX; [4]Rice Univ., Houston, TX

Abstract: High-density electrodes such as the Neuropixels probes provide an unprecedented ability to simultaneously record hundreds of neurons within local microcircuits. In addition to being widely adopted in animal models, recent work has also demonstrated the ability to translate this to record from the human brain in the intraoperative setup (Paulk et al, 2022; Chung et al, 2022). These studies focused on recording from cortical brain regions such as the frontal or temporal neocortex. Deeper structures including archicortex also play a critical role in

cognitive and affective processes. Previous human intracranial recordings have typically been limited to only a few neurons simultaneously, limiting assessment of network function. In our study, we extend previous research and successfully conduct high-density intraoperative recordings in not only the temporal neocortex of the middle temporal gyrus (MTG) but also the hippocampus (HC) in a patient undergoing an anterior temporal lobectomy. The recording was performed while the patient was under general anesthesia. We observed that the brain motion-induced drift was much smaller in the HC recordings compared to the MTG recordings - in the order of 10-100 μm in the HC recordings, compared to 100-300 μm in the MTG recordings. Perhaps due to the decreased motion or intrinsic firing patterns, our single and multi-unit yield was significantly higher in the HC. Using Kilosort 3.0 for spike sorting, we obtained a yield of ~100 units in the HC compared to ~50 units in the MTG. We will be refining this further using more advanced drift-correction steps to account for movement of the brain tissue. Ongoing work will also focus on improving our ability to localize the electrode, which will enable distinguishing the properties of single units across different HC subregions. This is one of the first attempts to characterize the physiological properties of neuronal responses in the human hippocampal local microcircuit.

Disclosures: S. Shah: None. **K.A. Katlowitz:** None. **J. Adkinson:** None. **R.K. Mathura:** None. **N.R. Provenza:** None. **N. Giridharan:** None. **G.P. Banks:** None. **L. Luan:** None. **C. Xie:** None. **A.J. Watrous:** None. **S.R. Heilbronner:** None. **A.M. Goldman:** None. **A. Maheshwari:** None. **B.Y. Hayden:** None. **S.A. Sheth:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.06/QQ11

Topic: H.07. Long-Term Memory

Support: NIH Grant K01MH111991
NIH Grant R01MH112613

Title: Hippocampal Novelty Signals Predict VTA Activation

Authors: *B. L. ELLIOTT, L. M. ELLMAN, V. P. MURTY;
Dept. of Psychology and Neurosci., Temple Univ., Philadelphia, PA

Abstract: Novelty is an important learning signal that is known to invigorate goal-oriented behavior via engagement of the mesolimbic dopamine (DA) system. Structurally, an afferent circuit with the hippocampus is crucial for regulating sustained signaling of VTA DA neurons. Specifically, animal research shows that HPC novelty signals lead to increased sustained mesolimbic engagement, which in turn magnifies phasic VTA responses to goal-relevant targets. However, the extent of these interactions during active human behavior remains unclear. To

address this gap, we employed a novel analysis of functional magnetic resonance imaging (fMRI) data from human subjects performing a target detection task intermixed with familiar and novel pictures. We found that activation to novel events in the anterior hippocampus dynamically predicted subsequent goal-relevant activation in the VTA on a segment-by-segment basis ($p<0.05$). Notably, as predicted by animal models, this relationship did not hold true for striatal novelty signals. This finding supports models of goal-oriented behavior in which hippocampal regulatory systems (i.e. hippocampus) in response to novelty invigorate VTA responsivity.

Disclosures: B.L. Elliott: None. **L.M. Ellman:** None. **V.P. Murty:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.07/QQ12

Topic: H.07. Long-Term Memory

Support: NIH/NIA Grant RF1 AG029577
UCSF REAC
UCSF Schwab DCDC Innovation Fund

Title: Voxelwise encoding models reveal complex semantic representations of social and emotional information in the anterior temporal lobes

Authors: *M. VISCONTI DI OLEGGIO CASTELLO[1], A. LEBEL[1], A. T. VU[2], K. P. RANKIN[2], J. L. GALLANT[1];
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Abstract: Cognitive disorders targeting the anterior temporal lobes (ATL) cause profound deficits in processing conceptual information. To better understand these disorders, it is crucial to understand the type of information represented in the ATL of neurotypical individuals. Previous functional magnetic resonance imaging (fMRI) studies investigating conceptual representations in the ATL, however, were limited by imaging and experimental methods. Most studies had reduced imaging coverage in the ATL, an area with large image distortions and low signal-to-noise ratio (SNR). Some task-based studies used optimized fMRI sequences to image the ATL, but they only probed a few semantic categories, recovering representations of only a handful of semantic concepts. To address these limitations, we developed a whole-brain 3T fMRI sequence optimized for imaging the ATL in individual participants, and we used voxelwise encoding models to recover participant-specific, high-dimensional maps of semantic representations in the ATL and across the whole cerebral cortex. Three participants listened to two hours of narrative stories from The Moth Radio Hour while their brain activity was measured using the novel ATL-optimized fMRI sequence. Features quantifying the semantic

content of the stimuli were extracted from the transcripts of the stories. These features were used to create voxelwise encoding models, which predicted the measured fMRI responses in each voxel and in each participant separately. The resulting model weights describe the tuning of each voxel to multiple semantic features. To create semantic maps describing voxel tuning across the cortex, the model weights were projected onto the three-dimensional group semantic space obtained from Huth et al. (2016), and then mapped onto the cortical surface of each participant. The results show that, in each participant, the ATL-optimized fMRI sequence produces high SNR and high model prediction accuracy across the ATL and the rest of the cerebral cortex. Across the three participants, the semantic maps reveal that the majority of significantly predicted voxels in the ATL are largely tuned to concepts related to people and emotions: 31-43% of voxels are tuned to "social" concepts (associated with words such as child, marriage), "communal" concepts (schools, community), or "professional" concepts (owner, worker); and 24-47% of voxels are tuned to "emotional" concepts (emotion, anger) or "mental" concepts (overwhelmed, memories). These results show that the ATL of neurotypical individuals preferentially encodes complex semantic representations of social and emotional information associated with natural speech.

Disclosures: M. Visconti di Oleggio Castello: None. **A. LeBel:** None. **A.T. Vu:** None. **K.P. Rankin:** None. **J.L. Gallant:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.08/QQ13

Topic: H.07. Long-Term Memory

Support: T32-MH019524
F32-MH114536

Title: Pupil variability tracks the stability of attention and hippocampal activity across time

Authors: *R. HUANG[1], D. V. CLEWETT[2];
[2]Psychology, [1]UCLA, Los Angeles, CA

Abstract: As we navigate everyday life, different features of our internal and external worlds cause attention to wax or wane. From time to time, the stream of experience is punctuated by event boundaries, or sudden context shifts, which evoke a momentary arousal response that perturbs overall attentional states. An interesting open question is whether these shifts in arousal also alter memory and contextual representations in the hippocampus, which plays an essential role in encoding and storing episodic memories. Using high-resolution functional magnetic resonance imaging (fMRI) in healthy young adults (N = 32, 22F), we investigated how attentional state fluctuations impact memory and the temporal stability of hippocampal

representations. Participants studied sequences of thirty-two object images while listening to auditory tones in either their left ear or right ear. To create a stable auditory context, or event, we played the same tone in the same ear for eight successive items. The tone then switched to the other ear, creating an auditory event boundary. This pattern of tone presentation then repeated for the remainder of the item sequence. To measure the temporal stability of attention, we measured variability in pupil diameter across time windows when auditory contextual information was either stable (i.e., repeated tones) or shifted (i.e., tone switches, or event boundaries). We found that pupil variability gradually increased across an entire item sequence, consistent with attentional instability due to time-on-task and fatigue effects. However, embedded within this broader effect, pupil variability gradually decreased within any given auditory event. These reductions in pupil variability within events were correlated with faster response times, suggesting that a stable event context facilitates sustained attention. Further, they were also related to less stable, or more similar, patterns of hippocampal subfield activation across time as well as better cumulative item encoding. Taken together, these findings suggest that attention dynamics modulate the temporal stability of hippocampal representations, especially when features of the external world remain stable. They also corroborate the use of pupil variability as a meaningful proxy for attentional stability across time.

Disclosures: **R. Huang:** None. **D.V. Clewett:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.09/QQ14

Topic: H.07. Long-Term Memory

Support: The Women's Board of Northwestern Memorial Hospital

Title: Cognitive and Neurobehavioral Impact of Stereoelectroencephalography (SEEG): A Prospective Cohort Pilot Study

Authors: *E. K. COTTON[1], E. CUNNINGHAM[1], J. ROSENOW[1], K. BANDT[1], R. VANPATTEN[2], K. MORDECAI[3], W. C. LAFRANCE[2], S. SCHUELE[1];
[1]Northwestern Univ., Chicago, IL; [2]Brown Univ., Providence, RI; [3]Univ. of Maryland, College Park, MD

Abstract: Rationale: This pilot study examines the cognitive and neurobehavioral effects of stereoelectroencephalography (SEEG), an invasive EEG monitoring method used in epilepsy evaluation. While SEEG is widely employed due to its low morbidity, the acute and chronic cognitive consequences remain unknown. Methods: Adult subjects undergoing SEEG at Northwestern Memorial Hospital were enrolled, excluding those with prior neurosurgical history. Participants completed neuropsychological assessments targeting frontal and mesial temporal

functioning two weeks after SEEG placement. Pre-surgical scores (generally obtained 6-12 months prior) served as baseline for comparison. Results: The study included 7 participants (6 males, 1 female) with varied seizure side and focus. Most post-SEEG neuropsychological scores, including digit span, design memory, verbal fluency, state/trait anxiety, and depression inventory, did not show significant changes. However, unexpected favorable improvements were observed in verbal memory performance, with statistically significant increases in CVLT-3 and LM scores. CVLT-3: SD Free Raw 8.7 ± 3.5 vs 11.4 ± 3.3, p=0.02; LD Free Raw 9.6 ± 3.5 vs. 12.3 ± 3.2, p=0.04; LMI Raw 24.7 ± 7.4 vs. 30.6 ± 8.3, p=0.03; and LMII Raw 19.7 ± 8.9 vs. 28.1 ± 8.7, p=0.01. These improvements should be interpreted cautiously due to potential practice effects, reliability metrics, and undetermined clinically meaningful change. Subjectively, following SEEG, 71% of participants reported sleep difficulty, 43% experienced depression/low mood, 29% reported irritability, and 14% noted agitation. These symptoms were new or worsened relative to pre-surgical baseline, and were gradually resolving by the 2-week post-op research visit. Conclusions: The findings suggest that circumscribed frontal/temporal cognitive performance and anxiety/depression mood disorder scores did not significantly decline two weeks after SEEG evaluation. However, subjective neurobehavioral symptoms of sleep impairment, irritability/agitation, and depression/low mood were reported immediately post-SEEG, gradually improving during the two-week recovery period. While these preliminary results are generally reassuring regarding cognitive and mood impacts, further comprehensive studies are needed. Patients should be counseled about the possibility of transient sleep difficulties, low mood, and agitation/irritability during the two weeks following SEEG.

Disclosures: E.K. Cotton: None. **E. Cunningham:** None. **J. Rosenow:** None. **K. Bandt:** None. **R. VanPatten:** None. **K. Mordecai:** None. **W.C. LaFrance:** None. **S. Schuele:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.10/Web Only

Topic: H.07. Long-Term Memory

Support: NIHM 7R01MH120194-02
NSF GRFP

Title: Exploring stimulation parameters and individual differences in amygdala-mediated memory modulation

Authors: *M. K. HOLLEARN[1], L. BLANPAIN[2], J. R. MANNS[4], S. B. HAMANN[4], K. BIJANKI[5], R. E. GROSS[4], D. L. DRANE[3], J. M. CAMPBELL[1], K. L. WAHLSTROM[1], J. T. WILLIE[6,7], C. S. INMAN[1];
[1]Univ. of Utah, Salt Lake City, UT; [2]Neurosci., [3]Neurol., Emory Univ. Sch. of Med., Atlanta,

GA; [4]Emory Univ., Atlanta, GA; [5]Neurosurg., Baylor Col. of Med., Houston, TX; [6]Neurosurg., Washington Univ., Saint Louis, MO; [7]Barnes-Jewish Hosp., Saint Louis, MO

Abstract: We previously have demonstrated that brief electrical stimulation to the basolateral amygdala (BLA) reliably enhances declarative memory in humans after a one-day delay without eliciting an emotional response. In addition, we have previously observed retrieval-based neural signals associated with prior BLA stimulation, like theta-gamma phase-amplitude coupling and coherence between medial temporal lobe (MTL) regions at the one-day delay. The present study aims to expand on our previous findings with 1) increased sample size and 2) examining the retrieval-based neural signals of prior BLA stimulation across the whole brain. We recruited 31 drug-resistant epilepsy patients undergoing stereo EEG surgery with depth electrode contacts implanted in various MLT regions. During continuous intracranial EEG recording, each participant was presented with a series of images of neutral objects. Across patients, we delivered a brief stimulation to the BLA (8 trains of 50-Hz pulses at 0.5 mA) before, during, or after image presentation and at varying stimulation duration to determine which stimulation parameters might best boost memory enhancement at the delayed test. Across all conditions, we found previously stimulated objects had more accurate recognition memory compared to previously non-stimulated objects ($t(30) = 2.90$, $p = .007$, $d = .44$). We included individual factors (e.g., baseline memory) and stimulation parameter factors (e.g., laterality of stimulation) into a multinomial regression model and found that baseline memory composed of neuropsychological long-term memory scores predicted stimulation responsiveness. Initial localization of precise stimulation site in the BLA suggests a role in determining responsiveness to stimulation, based on the location's proximity to other MTL regions like the hippocampus. The current results indicate that brief electrical stimulation to the human amygdala can enhance item-specific memory for neutral objects even in the absence of awareness of the stimulation, reflecting a key role of the amygdala in prioritizing experiences for long-term storage in declarative memory. Further inquiry in humans and experimental animals will be required to fully optimize the potential of amygdala-mediated memory enhancement. These studies may reveal the basic mechanisms of endogenous memory prioritization and yield insights into new memory-enhancing therapies.

Disclosures: M.K. Hollearn: None. **L. Blanpain:** None. **J.R. Manns:** None. **S.B. Hamann:** None. **K. Bijanki:** None. **R.E. Gross:** None. **D.L. Drane:** None. **J.M. Campbell:** None. **K.L. Wahlstrom:** None. **J.T. Willie:** None. **C.S. Inman:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.11/QQ16

Topic: H.07. Long-Term Memory

Support: NIH/NIA R01 AG070592

Title: Harmonized segmentation protocol of the hippocampal tail on high-resolution in vivo MRI from the Hippocampal Subfields Group

Authors: *N. GERVAIS[1], A. MAASS[2], J. SHINE[2], K. CANADA[3], E. MHAOLMHUAIGH[2], J. ADAMS[5], A. BAKKER[6], D. BERRON[2], V. CARR[7], M. DALTON[8], A. DAUGHERTY[4], R. LA JOIE[9], R. OLSEN[10], N. RAZ[11], C. E. STARK[12], L. WANG[13], L. WISSE[14], R. DE FLORES[15]; [1]Groningen Inst. for Evolutionary Life Sci., Univ. of Groningen, Groningen, Netherlands; [2]German Ctr. for Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [3]Wayne State Univ., Detroit, MI; [4]Wayne State Univ., Ypsilanti, MI; [5]UC Irvine, Irvine, CA; [6]Johns Hopkins Univ., Baltimore, MD; [7]San Jose State Univ., San Jose, CA; [8]Univ. of Sydney, Sydney, Australia; [9]Univ. of California San Francisco, San Francisco, CA; [10]Rotman Res. Inst., North York, ON, Canada; [11]Stony Brook Univ., Stony Brook, NY; [12]Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; [13]Psychiatry and Behavioral Hlth., The Ohio State Univ. Neurosci. Grad. Program, Columbus, OH; [14]Lund Univ., Lund, Sweden; [15]Caen-Normandy Univ., Caen, France

Abstract: Existing segmentation protocols for use on MRI scans and for boundaries of the hippocampus vary considerably across laboratories, particularly when considering subfields. Such variability leads to discrepancies in interpreting structural and functional neuroimaging results and when comparing them across studies. The Hippocampal Subfields Group (HSG) is an international organization addressing this issue by developing histologically valid, reliable, and freely available segmentation protocols for high-resolution T2-weighted 3T MRI. Currently, there is an existing protocol for the hippocampal body developed from multiple working groups. This protocol has reached consensus and passed reliability testing. However, it excludes slices containing the hippocampal tail due to the unreliability in detecting the stratum radiatum, lacunosum and moleculare (SLRM) layer, critical for identifying boundaries between subfields. Here, we describe the development of a distinct protocol for segmenting the hippocampal tail using *in vivo* 3T structural MRI. The segmentation protocol does not include subfields and is based on a novel histological reference data set labeled by multiple expert neuroanatomists. Four individuals within the tail working group developed boundary rules for the inferior, superior, medial, and lateral borders, and for identifying the anterior-most and posterior-most slices. Three raters subsequently segmented the hippocampal tail on scans from four individuals using the tail protocol and after reviewing detailed training materials. Two raters had relevant expertise, and one was a novice. While both expert raters achieved excellent reliability (between-rater intraclass correlation coefficient, or ICC= 0.995), reliability was low when considering the segmentations from the novice (ICC=0.543). Further analysis determined the lower reliability was the result of challenges the novice faced when identifying the anterior and posterior boundaries. When excluding the slices containing these boundaries, reliability was strong (ICC= 0.946). These findings suggest the protocol is appropriate for experts, with additional training required for novice users. The protocol will be shared as a manual and an automated segmentation protocol for wide adoption.

Disclosures: **N. Gervais:** None. **A. Maass:** None. **J. Shine:** None. **K. Canada:** None. **E. Mhaolmhuaigh:** None. **J. Adams:** None. **A. Bakker:** None. **D. Berron:** None. **V. Carr:** None. **M. Dalton:** None. **A. Daugherty:** None. **R. La Joie:** None. **R. Olsen:** None. **N. Raz:** None. **C.E. Stark:** None. **L. Wang:** None. **L. Wisse:** None. **R. De Flores:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.12/QQ17

Topic: H.07. Long-Term Memory

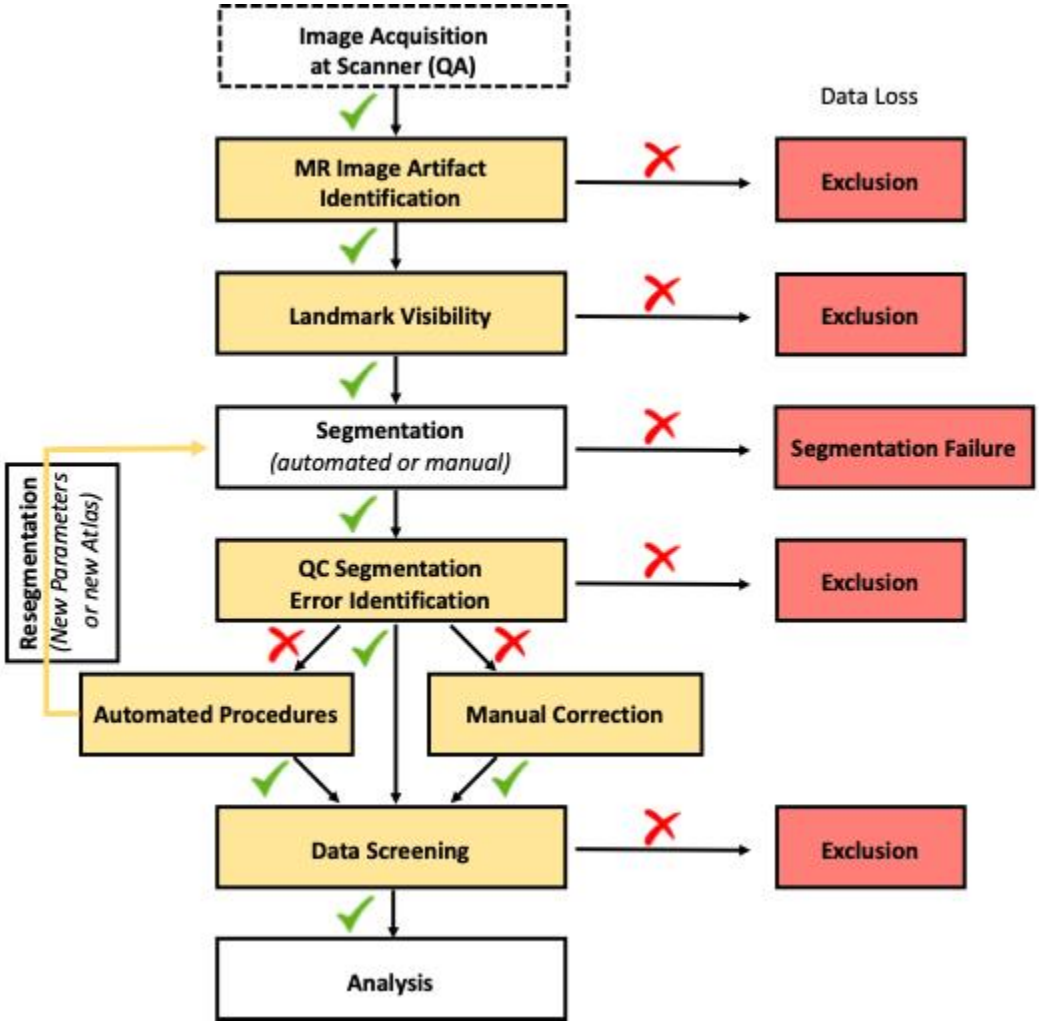
Support: NIH/NIA R01 AG070592
NIH/NICHD F32 HD108960

Title: Best practices for quality control of hippocampal subfield segmentations on T2-weighted MRI

Authors: *K. L. CANADA[1], N. MAZLOUM-FARZAGHI[2,3], G. RÅDMAN[4], R. K. OLSEN[3], L. E. M. WISSE[4], L. WANG[5], R. LA JOIE[6], P. A. YUSHKEVICH[7], J. N. ADAMS[8], A. BAKKER[10], D. BERRON[11], V. A. CARR[12], M. DALTON[13], R. DE FLORES[14], S. G. MUELLER[6], N. RAZ[15,16], C. E. STARK[9], A. M. DAUGHERTY[1];
[1]Wayne State Univ., Detroit, MI; [2]Univ. of Toronto, Toronto, ON, Canada; [3]Rotman Res. Inst., Baycrest Hlth. Sci., Toronto, ON, Canada; [4]Lund Univ., Lund, Sweden; [5]Psychiatry and Behavioral Hlth., The Ohio State Univ., Columbus, OH; [6]Univ. of California San Francisco, San Francisco, CA; [7]Univ. of Pennsylvania, Philadelphia, PA; [9]Neurobio. and Behavior, [8]Univ. of California Irvine, Irvine, CA; [10]Johns Hopkins Univ., Baltimore, MD; [11]German Ctr. for Neurodegenerative Dis., Magdeburg, Germany; [12]San Jose State Univ., San Jose, CA; [13]Univ. of Sydney, Sydney, Australia; [14]Univ. de Caen-Normandie, Caen, France; [15]Stony Brook Univ., Stony Brook, NY; [16]Max Planck Inst. for Human Develop., Berlin, Germany

Abstract: “Quality control” (QC) is a set of procedures for mitigating image processing errors and ensuring the validity and reliability of brain measurements. Despite its importance, there is little guidance on best QC practices and reporting procedures. The study of hippocampal subfields in vivo is a critical case for QC because of their small size, inter-dependent boundary definitions, and common artifacts in the MRI data used for subfields measurements. We addressed this gap by surveying the broader scientific community on their views and approaches to QC of hippocampal subfields. We received responses from 37 scientists from 10 countries, covering different career stages, and studying both healthy and pathological development and aging.In this sample, 81% of researchers considered QC to be very important or important, and 19% viewed it as fairly important. However, only 46% of researchers actually reported QC processes in prior publications. In many instances, lack of reporting appeared due to ambiguous guidance on relevant details and guidance for reporting, rather than absence of QC.Indeed, 95% of researchers reported rejecting data due to scan quality issues. We, therefore, provide operational definitions to standardize this procedure. Similarly, 95% of researchers indicated that they reviewed segmentations for errors and made judgments based on error severity, we provide a rating scale to inform these decisions. Notably, 74% of respondents corrected errors, but error correction rules varied among researchers.In the current work, we provide recommendations for correcting errors to maximize reliability and minimize bias. We also summarize threats to segmentation accuracy, review common QC methods, and make recommendations for best

practices and reporting in publications (Fig. 1). Identifying and correcting errors in segmentations ensures measurement validity and prioritizes data retention. Thus, implementing the recommended QC practices will collectively improve inferences to the larger population, as well as have implications for clinical practice and public health.



Disclosures: K.L. Canada: None. **N. Mazloum-Farzaghi:** None. **G. Rådman:** None. **R.K. Olsen:** None. **L.E.M. Wisse:** None. **L. Wang:** None. **R. La Joie:** None. **P.A. Yushkevich:** None. **J.N. Adams:** None. **A. Bakker:** None. **D. Berron:** None. **V.A. Carr:** None. **M. Dalton:** None. **R. de Flores:** None. **S.G. Mueller:** None. **N. Raz:** None. **C.E. Stark:** None. **A.M. Daugherty:** None.

Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.13/QQ18

Topic: H.07. Long-Term Memory

Support: NIH/NIA R01 AG070592

Title: Reliable consensus protocol to segment subfields within the hippocampal body on high-resolution in vivo MRI from the Hippocampal Subfields Group

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Abstract: Hippocampal subfields differentially develop and age at different paces, and vary in vulnerability to neurodegenerative diseases. Innovation in high-resolution imaging has accelerated clinical research on hippocampal subfields but substantial differences in segmentation protocols impede comparisons across laboratories. The Hippocampal Subfields Group (HSG) is an international organization seeking to address this issue by developing a histologically-valid, reliable, and freely available segmentation protocol for high-resolution T2-weighted 3T MRI (http://www.hippocampalsubfields.com). Collaboration of multiple HSG working groups has produced a consensus segmentation protocol that passed reliability testing. The segmentation protocol is based on a novel histological reference data set labeled by multiple expert neuroanatomists. Twenty-six labs with at least 4 years experience segmenting hippocampal subfields participated in an online survey, which included detailed protocol information, feasibility testing, demonstration videos, example segmentations, and labeled histology. Labs rated each internal boundary definition for clarity and agreement with the protocol on a 1 (low) to 9 (high) scale. All definitions were rated with high clarity (M = 8.42 -

8.65) and reached consensus agreement (binomial ps < 0.01). The consensus protocol includes labels for the internal boundaries between subiculum, Cornu Ammonis (CA) 1-3 fields, and dentate gyrus following a geometric heuristic that, when combined with the external boundaries that previously reached consensus, labels subfield volumes throughout the hippocampal body. Using detailed training documentation, 3 raters naïve to the protocol (2 with relevant expertise and 1 novice) achieved good reliability: between-rater intraclass correlation coefficient = 0.7-0.9, and within-rater = 0.8-0.9. The consensus protocol will be shared as a manual and an automated segmentation protocol for wide adoption in the research community. Additional definitions for subfields in hippocampal head, a hippocampus tail label, and medial temporal lobe cortices are in development. The consensus protocol will significantly facilitate cross-study comparisons and provide increased insight into the structure and function of hippocampal subfields across the lifespan and in neurodegenerative diseases.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.14/QQ19

Topic: H.07. Long-Term Memory

Support: NIH U01NS117839
Simons Foundation Collaboration on the Global Brain (542941)
Caltech NIMH Conte Center P50MH094258

Title: Abstract representations encoded by human hippocampal neurons support inference behavior and can be induced through verbal instruction

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Abstract: Cognitive task variables are frequently represented in a distributed manner across large populations of neurons, with information being encoded and organized in a manner that eludes traditional univariate single-neuron analysis. Recent developments in the theory and measurement of population-level task representations have provided evidence that animal brains can construct representations that are simultaneously high dimensional and encode variables in an abstract format - a signature of low dimensionality. These features of representations support behavioral flexibility and generalization, and are crucial for successful execution of complex cognitive tasks. However, to date, relatively few studies have explored the role of representational geometry in shaping computation in the human brain at the single neuron level, and no study has, to our knowledge, studied the emergence and manipulation of this geometry on short timescales. To study the relationship between representational geometry and behavior, we conducted neuronal recordings in the brains of epilepsy patients performing inferential reasoning during a serial reversal learning task. Reversals were uncued, giving rise to a latent contextual variable that could be utilized by subjects to perform inference. Patients (17 total) completed 36 task sessions (280-320 trials/session, 10-16 blocks/session). Responses of single neurons were recorded using hybrid clinical-research electrodes during these sessions, yielding 2694 well isolated neurons from structures throughout the temporal lobe and frontal cortex. We found that changes in representational geometry at the level of the neural population in the hippocampus alone supported inference behavior. The hippocampus exhibited 1) an increase in representational dimensionality, and 2) coded for multiple variables simultaneously, including an explicit representation of the latent context variable, in an abstract format. Furthermore, we found that behavioral intervention with verbal instructions was sufficient to induce these changes in hippocampal representational geometry that were necessary for successfully performing inference.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.15/QQ20

Topic: H.07. Long-Term Memory

Support: NIH Grant U01NS117839

Title: Human medial temporal lobe and medial frontal cortex neurons represent metacognitive confidence judgments in a domain-specific manner across recognition memory and visual discrimination tests

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Abstract: Much debate surrounds whether the neural substrate of metacognitive decisions (here, confidence judgments) is domain-general or domain-specific, particularly between memory and perceptual domains. To begin to assess the domain-generality of metacognition, we developed a new task that has both a recognition memory and visual discrimination part. Both parts were tightly controlled to equalize task structure and difficulty. Participants initially studied a series of images, each containing 100 randomly inserted red or blue dots. During the test phase, participants viewed each image for 1 s, then decided whether the image appeared during the study phase (recognition memory) or if the image contained more red or blue dots (visual discrimination). Each response required a simultaneous confidence judgment (either 'high' or 'low'). In a behavioral experiment of 153 participants, we found a strong cross-task relationship in metacognitive bias ($r_{(151)} = .73$), but no significant relationship in metacognitive efficiency ($r_{(151)} = .05$). This suggests that individual tendencies to respond with high confidence represents a domain-general process, whereas the ability to accurately assign high confidence to correct responses is domain-specific. We piloted this experiment in four epilepsy patients with depth-electrode implants and obtained single-unit recordings across various medial temporal lobe (MTL) and medial frontal cortex (MFC) regions. To identify confidence-selective neurons, we assessed differences in firing rates between test trials rated with high versus low confidence during the stimulus presentation period. We found confidence-selective cells in 31/223 (14%) MTL and 21/176 (12%) MFC neurons. Of the 52 identified confidence-selective neurons, only two showed selectivity in both tasks whereas the other 50 remained task-specific (i.e. only 4% of confidence-selective neurons showed domain-generality). For comparison, we identified visually-selective neurons, which exhibit an increased firing rate to a particular image category, in 65/223 (29%) MTL and 19/176 (11%) MFC neurons. Despite the fact that image category is irrelevant for the visual discrimination task, a large proportion of visually-selective neurons proved to be selective in both tasks (36/65 in the MTL and 10/19 in the MFC, or 52% total). This suggests that the substrate supporting metacognitive judgments is largely represented in a domain-specific manner between recognition memory and visual discrimination tests at the single-unit level in the MTL and MFC.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.16/QQ21

Topic: H.07. Long-Term Memory

Support: Simons Collaboration on the Global Brain
NIH U01 grant (U01NS117839)

Title: Distinct populations of neurons track item familiarity and source context in the human medial temporal lobe

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Abstract: Memory research has long debated whether familiarity for an item itself and its source context rely on a common neural substrate. Whereas single process theory posits that a common memory strength signal accounts for both types of memory, dual process theory posits that distinct systems subserve the two. Here, we leverage single-unit recordings from the medial temporal lobe (MTL) and medial frontal cortex (MFC) in human patients to show that familiarity and source memory appear to rely on distinct processes.
Using a cued recall task, 7 patients undergoing epilepsy monitoring were presented with 72 faces twice. Memory was tested 5 minutes later using 36 novel and the 72 previously encoded faces as retrieval cues. During encoding period, each face was associated with a specific source context, either a perceptual or social judgment (roundness or talkativeness, respectively, on a 1-5 scale). During memory retrieval period, patients made new/old judgments for face familiarity, followed by source context judgments for reported old faces. Behaviorally, patients performed reasonably well on both item familiarity and source context memory, although slightly lower than a healthy comparison group (AUC of 0.85±0.14 and 0.72±0.11 for patients; AUC of 0.95±0.04 and 0.84±0.08 for the comparison group, N=15).
Of the recorded single neurons in the MTL, 17% (39 out of 230) exhibited statistically significant differences in firing rates ($p<0.05$) between novel and familiar faces during retrieval (0.2-2.2 sec window). Two distinct populations of cells represented source context information during encoding and retrieval periods. Encoding-related source context cells were found in both MTL (11%, 26 out of 230) and MFC (16%, 25 out of 156) regions. During retrieval, only amygdala neurons (9%, 14 out of 154) were sensitive to source context. Notably, there was no overlap between cells differentiating novel/familiar faces and those differentiating source context during retrieval. Preliminary analyses using population decoding yielded consistent results.
Our findings support the dual process theory of recognition memory, with distinct neural processes underlying familiarity and source memory. Moreover, the representation of source context during encoding and retrieval involved separate populations of cells, indicating different engagement between contextual reinstatement and encoding. However, our conclusions are limited by the small patient sample and brain regions recorded. Furthermore, the generalizability of these results to objects other than faces remains an open question.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR108.17/QQ22

Topic: H.07. Long-Term Memory

Support: NIH U01NS117839
NIH K99NS126233

Title: Prefrontal and Medial Temporal Neurons Encode Ordinal Information of Event Sequence in Humans

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Abstract: Remembering the temporal order of events is critical for episodic memory. Previous studies suggest linking individual events into temporally associated memories relies on the medial temporal lobe and prefrontal cortex. Damage or losses to these regions can disrupt the recall of stories and real-life events in the correct temporal sequence. Despite the critical role of the medial temporal lobe and prefrontal cortex in episodic memory, little is known about how ordinal information is encoded and later retrieved in these regions. To address this question, we recorded single-neuron activity and local field potential signals with depth electrodes implanted in 12 drug-resistant epilepsy patients for diagnostic purposes. Participants first watched 25 video clips with no audio. Each clip contained four events, with visual cuts either inserted at event boundaries, away from boundaries, or without visual cuts. Participants' memory of clip content was subsequently evaluated in two memory tests. In the scene recognition task, participants identified whether a frame was familiar (from watched clips) or not (from unseen clips). In the time discrimination task, participants determined which event happened first when presented with two frames associated with the tested events. Behaviorally, participants had comparable recognition memory regardless of the clip type but had more accurate order memory for frame pairs extracted from clips with visual cuts at event boundaries. We recorded 634 neurons in total. At the single cell level, we found neurons in the hippocampus (6%), amygdala (5%), and orbitofrontal cortex (7%) that transiently increased their firing rates selectively following a specific ordered event boundary (e.g., 2nd event boundary in a four-event clip) relative to clip onset, invariant to event contents. At the population level, hippocampal and prefrontal theta power after event boundaries increased along with event orders while the frequency of theta oscillations decreased. Further, transient theta phase precession was observed following event boundaries, with its strength modulated by event order. In sum, our results suggest that the

medial temporal lobe and prefrontal cortex employ multiple neural coding mechanisms at both the single cell and population levels to index sequential order in memory.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

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Program #/Poster #: PSTR108.18/QQ23

Topic: H.07. Long-Term Memory

Support: Brain Initiative NIH grant U01NS103792
Brain Initiative NIH grant U01NS117839

Title: Evidence accumulation by human Medial Temporal Lobe neurons during memory-based decisions

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Abstract: How we integrate mnemonic information of declarative memories to make memory-based decisions (MBD) is unknown. We hypothesize that neurons in Medial Temporal Lobe (MTL) areas in humans integrate memory-derived evidence. We conducted behavioral experiments, modelling, and human single neuron recordings to examine this question. We recorded from 2068 single neurons in the MTL of 30 epileptic patients across 39 sessions. Subjects viewed faces partially masked by a 2D Gaussian “bubbles” mask to cover parts of the face and rated the faces as Old or New. Reaction time, accuracy, and confidence scaled with difficulty, which was modulated parametrically by the proportion of the faces masked by the noise mask. We fit drift diffusion models (DDM) to the behavior. A model with parameters drift rate, threshold, starting point, and non decision time, with parameters drift rate and non-decision time vary by condition (new/old, easy/hard) explained the behavior best. 215 neurons responded differently to Old vs. New stimuli. We focused our analyses on the subset of N=54 of these memory selective neurons that increased their response for Old relative to New stimuli with a

mean firing rate greater than 0.5 Hz. The dynamics of the neural response of memory selective cells to old stimuli was systematically related to the parameters of the DDM model in each subject: the slope of firing rate increase correlated with drift rate, and the time till firing differed from baseline correlated with the non-decision time. To further examine this, we next decoded the memory-based decision (Old or New) from the entire population of all recorded neurons. We found that decoding accuracies were higher for easy compared to hard trials. Like the single-neuron result, the dynamics of decoding accuracy were systematically related to drift rate and non decision time. We observed the rate of increase in decoding accuracy was slower for hard trials and the time till the decoding accuracy differed from baseline was shorter for easy trials. Lastly, we used dPCA to examine the dynamics in neural state space. We found the speed at which the neural state changed was higher for easy trials and for decision components compared to ground truth. Furthermore, we found non decision times in neural state space also modulated by difficulty. Moreover, memory selective cells contributed more to these population effects. Together, these findings show that the dynamics of neural activity in the human MTL during memory retrieval can be predicted by a DDM model fit to an individual subject behavior. This data therefore shows evidence that human MTL neurons can be conceptualized as integrators of information retrieved from memory during MBD.

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Poster

PSTR108. Medial Temporal Lobe and Human Long-Term Memory: Brain Stimulation and Neurophysiology

Location: WCC Halls A-C

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Topic: H.07. Long-Term Memory

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Simons Collaboration on the Global Brain
NIH Grant T32 NS105595-01A1

Title: Neurons in human medial temporal lobe encode semantic dimensions of movies

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Abstract: The human medial temporal lobe (MTL) is critical for episodic memory. Previous single-neuron studies in the MTL have identified a number of neuron types associated with

episodic representation, including concept cells, semantic cells, novelty and familiarity cells, time cells, and event boundary cells. These findings were typically obtained using static visual stimuli in artificial task paradigms, and may not fully capture the neurons' function in naturalistic dynamic contexts. How MTL neurons encode experiences of dynamic stimuli remains unclear. To investigate this question we recorded intracranial EEG activity from 16 patients (age 17-67, 10 female) as they viewed an edited 8-minute version of the Alfred Hitchcock Presents episode "Bang! You're Dead." We recorded 1457 neurons across 29 sessions. In order to quantitatively capture the visual and semantic features of our naturalistic stimuli we extracted frame-wise features using pictorial (ResNet50) and semantic (CLIP) deep learning models and trained a decoder to predict these features from the neural data. We find that neurons in the medial temporal lobe have significantly better decoding accuracy for CLIP features compared to ResNet features. Our findings suggest that these neurons are tuned to semantic, rather than pictorial features. We find that particular neurons are essential for recording specific semantic dimensions, i.e. have a 'semantic receptive field.' Together, these results suggest that MTL neurons represent semantic meaning during naturalistic movie viewing.

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Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.01/QQ25

Topic: H.08. Learning and Memory

Support: ERC-ST2019 850769
PCEGP3_194220

Title: Learning leads to the formation of multiple memory traces in the mouse hippocampus

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Abstract: With time, memories of personal experiences change. While early on they are rich in details and able to integrate new information upon shifts in contingencies, as time goes by, memories become generalized and resistant to updating. Similarly, the biological substrate of a memory (known as its "engram") goes through a profound reorganization, and distinct cortical and subcortical circuits are recruited upon memory retrieval as a function of the delay between acquisition and recall. Some brain regions, such as the hippocampus, are however involved in multiple memory processes including memory acquisition, consolidation, recent and remote recall. A fundamental open question remains as to whether specific hippocampal subpopulations support each of these functions or if the same neurons are recruited at all times. Here we leveraged a developmental framework to target functionally distinct subpopulations of

hippocampal principal neurons, and investigated their recruitment and functionality in the hippocampal engram over time. Our results show that (1) distinct subpopulations of developmentally-defined neurons have distinct contributions to the engram during memory consolidation, recent and remote recall; (2) their activation at specific delays after acquisition is necessary for successful memory retrieval; (3) a subpopulation with a transient reactivation profile is necessary for the long-term permanence of the memory; and (4) the recruitment of a transient memory trace supports plasticity of recently-acquired memories. Together, our results indicate that multiple memory traces are laid down in the hippocampal engram during memory encoding, each with its own maturation, reactivation, and permanence dynamics. Thus, we reveal that the interplay between a transient and a permanent memory traces regulates the closure of a temporally-limited window for memory plasticity in the days after encoding.

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Poster

PSTR109. Hippocampal Formation Circuitry II

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Program #/Poster #: PSTR109.02/QQ26

Topic: H.08. Learning and Memory

Support: European Research Council Starting Grant (ERC_ST2019 850769)
Exccellenza Grant from the Siwss National Science Foundation (PCEGP3_194220)

Title: Opencabmi: an open source software toolbox for two-photon brain-machine-interface control

Authors: *C. MITELUT[1], A. DE VICENTE[2], **R. AUGOSTO VIANA MENDES**[2], M. COLOMER[2], F. DONATO[3];
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Abstract: Brain machine interfaces (BMIs) are a promising tool for studying the restoration of mobility in human patients with paralysis and a promising tool for understanding the neural correlates of learning. BMIs have been implemented in human and non-human primates and recently been adapted for use in mice via extracellular electrophysiology and two-photon calcium (2P) recording techniques. 2P imaging approaches for BMIs offer advantages such as identifying the same cells longitudinally, targeting and characterizing specific neuronal populations using viral and genetic techniques but currently require expensive software packages and the merging of 2P software algorithms with BMI algorithms. Here we present OpenCaBMI ("OpenCaB"), an open source software package that integrates the preprocessing of raw 2P [ca] signals with online learning and rewarded behavior algorithms. OpenCaB can integrate with any

2P system that saves data in realtime and requires only realtime access to two-photon data via a hard-disk location and (optionally) a TTL pulse. OpenCaB can achieve speeds of up to 200 frames per second (or more) and comes with python notebooks that are simple to use and customize. The python scripts assist the user in selecting ROIs for real-time tracking and automatically selecting thresholds for rewarded behaviors. The toolbox comes with a graphical-user-interface (GUI) that provides real-time tracking of single neuron and ensemble activity, the behavior of the animal, the active FOV of the two-photon system and the frequency of a real-time feedback signal such as speaker tone. Additionally we provide options for manual and automated drift tracking. Finally, OpenCaB comes with a simulation-only version allowing for easy integration, testing and debugging even without an available or active two-photon system. We implemented OpenCaB in a water-rewarded BMI task using neurons from the mouse motor cortex and hippocampus CA3 area and established mouse learning over a period of 8 days.

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Poster

PSTR109. Hippocampal Formation Circuitry II

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Program #/Poster #: PSTR109.03/QQ27

Topic: H.08. Learning and Memory

Support: ERC-ST2019 850769
PCEGP3_194220

Title: Circuit mechanisms for the reinstatement of infantile memories

Authors: *M. LAHR, F. IMHOF, T. ULMER, F. DONATO;
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Abstract: Memories of everyday life, that is episodes of where, when, and what happened to us, are formed and stored in the hippocampus as groups of neurons that exhibit correlated activity - also known as neuronal ensembles or engrams. Reactivation of the ensembles by natural cues can induce memory retrieval and elicit appropriate behavior even at long time delays from the original encoding. In stark contrast, memories formed early in infancy are often rapidly forgotten. This phenomenon of accelerated forgetting is called infantile amnesia, and is found in humans as well as non-human species like rodents. Previous studies showed that although infantile memories cannot be retrieved by natural cues later in life, artificial optogenetic stimulation of infantile memory ensembles can re-induce according behavioral responses, indicating the persistence of a silent memory trace through time. In our study, we ask whether infant learning in mice leads to the formation of a neuronal ensemble in the hippocampus, if this ensemble is stable from infancy to adulthood, and if “forgotten” silent memory traces influence memory processes in the adult. To tackle these questions, we use contextual fear conditioning as

learning paradigm, and permanently genetically tag active ensembles to visualize and manipulate infant memory traces through the lifespan. Our results show that a stable memory trace persists from infancy to adulthood, and that animals have the potential to use these silent infant memory traces for memory reinstatement and to facilitate learning of similar events and their assimilation into pre-existing knowledge structures. Taken together, our results point towards a very specific function of silent infant memory engrams in the adult brain, and might inform strategies to prevent the reinstatement of memories related to traumatic infant events.

Disclosures: M. Lahr: None. **F. Imhof:** None. **T. Ulmer:** None. **F. Donato:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.04/QQ28

Topic: H.08. Learning and Memory

Support: Canadian Institutes of Health Research (CIHR)
Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Hippocampal CA1 VIP interneurons detect novelty in the environment and regulate recognition memory

Authors: *S. TAMBOLI[1], S. SINGH[2], P. YASHCHUK[2], M. BARKAT[2], D. TOPOLNIK[2], A. GUET-MCCREIGHT[3], L. TOPOLNIK[2];
[1]Dept. of Biochemistry, Microbiology and Bio-informatics, CRCHUQ-CHUL, Univ. Laval, Université Laval, QC, Canada; [2]Dept. of Biochemistry, Microbiology and Bio-informatics, CRCHUQ-CHUL, Université Laval, QC, Canada; [3]Krembil Ctr. for Neuroinformatics, Univ. of Toronto, Toronto, ON, Canada

Abstract: In the CA1 hippocampus, vasoactive intestinal polypeptide-expressing interneurons (VIP-INs) make complex connectivity motifs by targeting GABAergic cells and pyramidal neurons (PYRs). The resulting inhibitory and disinhibitory circuit interactions can regulate memory processing, but the specific role of VIP-INs in this process remains poorly understood. In this study, we combined in vivo calcium imaging and optogenetic manipulations in freely behaving mice to reveal the role of VIP-INs in episodic memory processing. To examine whether VIP-IN activity can shape the activity dynamics of their downstream targets, we also conducted in vivo calcium imaging of PYRs and major IN types in CA1 - somatostatin (SST) and parvalbumin (PV) expressing interneurons. In the contextual memory task, VIP-INs showed increased activity when mice traveled from a familiar environmental context to a new one. Further, in the object memory task, the activity of these cells increased during object exploration and was even higher during the exploration of novel and spatially displaced objects. Interestingly, PYRs exhibited a similar activity trend i.e., positive modulation in response to novel context and objects, whereas SST and PV-INs activity did not alter significantly in

response to these stimuli. In addition, the role of VIP-INs in object memory was studied using a closed-loop optogenetic inhibition of VIP-INs specifically in the object zones during the encoding phase of the object memory task. The data revealed compromised object recognition memory, thus highlighting the crucial role of VIP-INs in memory encoding. Ongoing experiments with optogenetic inhibition of VIP-INs during the recall phase will provide evidence of the involvement of VIP-INs in memory retrieval. In summary, these data indicate that CA1 VIP-INs respond to novelty in the environment and via circuit disinhibition may aid in encoding episodic memory and adaptive behaviors.

Disclosures: **S. Tamboli:** None. **S. Singh:** None. **P. Yashchuk:** None. **M. Barkat:** None. **D. Topolnik:** None. **A. Guet-McCreight:** None. **L. Topolnik:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.05/RR1

Topic: H.08. Learning and Memory

Title: Exploring the relation between phenomenal and functional properties in hippocampal episodic memory processing through a spiking neural network.

Authors: *G. KIM, P. KIM;
Mathematics, Ulsan Natl. Inst. of Sci. and Technol. (UNIST), Ulju-gun, Korea, Republic of

Abstract: During hippocampal episodic memory processing, information is rapidly stored, and retrieved firing patterns are compressed which is known as theta precession and replay during theta oscillation and sharp wave ripples (SWR) respectively. There are various computational studies provided insights into the underlying mechanisms, but the connection between these phenomenal properties and functional properties like pattern separation and pattern completion, remains unclear. Using a spiking neural network, we investigated how the functional properties can naturally integrate with the phenomenal properties within the hippocampus. Our model is based on the hippocampal circuitry, with the assumption that theta oscillation repetitively cycles between an encoding phase and a retrieval phase. We simplified the dentate gyrus (DG) to perform instant spatial pattern separation when the superficial entorhinal cortex (EC) sends vector sequences during encoding. The separated information is then transmitted to CA3, where heterosynaptic plasticity allows for the storage of information from the perforant path to CA3 pyramidal neurons originating from the superficial EC, recurrent collateral, and Schaffer collateral. This mechanism encodes various vector sequences in a sparse distributed form within CA3, regardless of the similarity between the sequences. Additionally, CA1 receives the same vector sequences from the deep EC, facilitating the reinstatement of the original vector sequences encoded in CA3. During retrieval, one engram, determined by the similarity between external inputs and the information stored in each engram through the perforant path to CA3 from the superficial EC, is activated via a winner-takes-all mechanism facilitated by global

inhibition. These winner engrams reinstate the encoded information through CA1 and the deep EC, effectively preventing interference. Furthermore, the engram firing patterns exhibit a compressed form that aligns with phase precession and SWR. Our findings suggest that the coordination of hyperpolarization during the encoding phase of theta oscillation, short-term plasticity, and adaptation mechanisms is crucial for demonstrating the replay phenomenon in both online and offline states. Intriguingly, we also observed the emergence of new combined sequences during replay, suggesting that the hippocampal processing is not limited by context and may be involved in divergent thinking. This study contributes to our understanding of memory formation and retrieval processes by elucidating the relation between phenomenal properties and the functional properties of hippocampal episodic memory processing.

Disclosures: G. Kim: None. **P. Kim:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.06/RR2

Topic: H.08. Learning and Memory

Title: Processing space and non-space in the enclosed and the exposed blades of the dentate gyrus and their relationship with the CA1-CA3 proximodistal hippocampal subnetworks

Authors: *R. KAYUMOVA, E. ATUCHA, M. SAUVAGE;
Leibniz Inst. for Neurobio., Magdeburg, Germany

Abstract: Recent anatomical and IEG imaging studies indicate that spatial and non-spatial information, which form episodic memories, might be processed by distinct subnetworks segregated along the proximodistal axis of the hippocampus (Ku et al, 2022 SfN abstract; Beer and Vavra et al, 2018; Flasbeck et al, 2018; Nakamura et al, 2013). This could especially be the case when one dimension of the memory (spatial or non-spatial) is overly relevant compared to the other and the integration of the least relevant information dispensable. The enclosed blade (suprapyramidal) of the Dentate Gyrus (DG), distal CA3 and proximal CA1 (both close to CA2) constitute the spatial subnetwork. The non-spatial subnetwork, on the other hand, consists of the exposed blade (infrapyramidal) of the DG, proximal CA3 (close to the DG), and distal CA1 (close to the subiculum). Functional data supporting the existence of these subnetworks are, however, only available for CA1 and CA3. Using optogenetics in murine spatial and object pattern separation tasks, we recently showed that the enclosed blade preferentially processes spatial information while the exposed blade has stronger ties to the non-spatial domain (Kayumova et al, 2022 SfN). Whether the enclosed blade is a part of the spatial subnetwork and whether the exposed blade belongs to the non-spatial one, remains however untested. To address these questions, we used *Arc* imaging to investigate the activity of the CA1-CA3 subareas that part of the spatial and non-spatial subnetworks upon optogenetic silencing of the enclosed or the exposed blade of the DG. Preliminary data indicates that the inhibition of the enclosed blade

affects the balance between the recruitment of the spatial and the non-spatial subnetworks, which correlates with deficits in spatial memory. Inhibiting the exposed blade also influences the activity of the downstream CA1-CA3 subnetworks, albeit in a different manner, and led to impaired non-spatial memory. Altogether, these results indicate that the enclosed and the exposed blades of the DG are indeed part of distinct hippocampal subnetworks with differing preference for spatial and non-spatial information processing.

Disclosures: **R. Kayumova:** None. **E. Atucha:** None. **M. Sauvage:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.07/RR3

Topic: H.08. Learning and Memory

Support: KIST Grant 2E32211
NRF 2021R1A2C3005560
NRF 2019R1A6A3A01096971

Title: Memory trace of a virtual butterfly encounter

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[1]Korea Inst. of Sci. and Technology(Kist), Seoul, Korea, Republic of; [2]Korea Institude of Sci. and Technology(Kist), Seoul, Korea, Republic of

Abstract: Episodic memory is necessary for animals to adapt to the dynamically changing world. The hippocampus plays a critical role for storing diverse episodic information such as the place, objects, people and temporal sequence of an event. The underlying mechanisms of episodic memory encoding, storage and retrieval have largely been investigated by examining the changes in hippocampal cell activity following the exposure of rodents to novels environments. However, this approach poses a challenge for the investigation of memory dynamics at higher temporal resolution. To address this issue, we developed a new paradigm in which mice run head-fixed on a cue-enriched treadmill and occasionally encounter a butterfly dummy controlled by 3-motor-axes. We recorded hippocampal CA1 and CA3 neuron responses using silicon probe. We observed that the very first encounter of the butterfly could alter place cell activity in either a transient or persistent manner. A neural network model of competitive learning replicated the spectrum of place cell responses and revealed a parallel development of engrams for spatial environment and butterfly encounter. These findings demonstrate the existence of hippocampal memory traces for single encounters and provide insights on neural network mechanisms underlying ‘1-shot’ encoding of episodic memory.

Disclosures: **D. Jung:** None. **D. Jung:** None. **S. Royer:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.08/RR4

Topic: H.08. Learning and Memory

Title: Prioritizing replay when future goals are unknown

Authors: *Y. SAGIV[1], T. AKAM[2], I. B. WITTEN[1], N. D. DAW[1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: The ability to connect actions to their long-term consequences is key for intelligent behavior. Recently, significant attention has been paid to nonlocal “replay” trajectories in hippocampus and prefrontal cortex as a mechanism by which this might be accomplished. Nevertheless, the specific computational function of these events remains elusive. One hypothesis holds that replay plans routes to current goals by propagating reward information over space in order to create value functions that drive behavior. An alternative view contends that replay learns and maintains routes more generally, separate from current goals or plans, to update a “cognitive map” of the environment. The former view has been formalized in a reinforcement learning framework (Mattar and Daw 2018) that predicts which trajectories should be replayed preferentially (“prioritized”) to best support planning. However, recent data appear to contradict this perspective, showing a disconnect between replayed destinations and current goals (Gillespie et al. 2021, Carey et al. 2018), and no similar theory exists to formalize the alternative perspective. Here, we generalize the Mattar account to address replay for a map of routes to many locations (a variant of the successor representation), when which of these contain reward is unknown or expected to change in the future. This leads to a prioritization strategy that evaluates candidate trajectories for replay according to a learned distribution over possible future goal locations, rather than with respect to the current reward function. We show that replay in an agent with this objective explains experimental results in which replay is systematically focused on different goals than the animal's current behavior. Furthermore, we provide predictions for replay dynamics under a novel task paradigm concerned with testing the effect of environmental goal statistics on the prioritization of goals. We suggest that our model provides a new framework for understanding how replay in the brain can facilitate flexible behavior in dynamic environments by the efficient construction and updating of cognitive maps.

Disclosures: Y. Sagiv: None. **T. Akam:** None. **I.B. Witten:** None. **N.D. Daw:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.09/RR5

Topic: H.08. Learning and Memory

Title: Imaging (more) naturalistic memories over half a lifetime using 9.4T fMRI in awake rats

Authors: L. MAHNKE[1], E. ATUCHA[1], P. VAVRA[2], Y.-H. CHANG[1], P. WENK[1], F. ANGENSTEIN[3], ***M. SAUVAGE**[1];
[1]Leibniz Inst. for Neurobio., Magdeburg, Germany; [2]Dept. of Biol. Psychology, Otto von Guericke University, Med. Fac., Magdeburg, Germany; [3]Deutsches Zentrum Für Neurodegenerative Erkrankungen (DZNE), Magdeburg, Germany

Abstract: In humans, memory is typically investigated using fMRI. The hippocampus (HIP) is crucial for retrieving memories. High-resolution immediate-early gene imaging studies in rodents have shown that the CA3 subfield of the HIP is no longer involved in retrieving memories when they age (i.e. when they reach 6 months to 1-year-old, comparable to 20- and 40-year-old memories in humans, based on life expectancy; Lux et al., eLife, 2016). Further, this coincides with the loss of memory precision (Atucha et al., BioRxiv, 2021). In a laboratory setting, measuring episodic memory involves the creation of a unique event and its retrieval at a later time point. However, real-life events, even unique, include elements that reoccur over the life span. For example, seeing again your bike days after experiencing a bad bike fall. As a first step for evaluating whether CA3 is also disengaged in a more naturalistic setting (i.e. when features of a given memory are re-experienced over the life span), we designed a new 9.4T fMRI-compatible task for awake rats. This task was used to repeatedly image the BOLD signal occurring during the retrieval of an auditory-fear conditioning memory while mimicking the passive reoccurrence of elements of this memory. This was done by delivering 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year after the formation of a tone-footshock association the conditioning tone (1 kHz; associated with a mild footshock after a trace interval) and a tone that had not been experienced by the rats (a neutral tone). Preliminary data show a stronger hippocampal BOLD activation for the trace than the tone period in some of the 'shock group' animals when the memory was recent (1 day old; 'trace>tone' contrast). Yet, no such pattern could be detected for early remote memories (1-month-old memories), although memories had been retained in both cases (after 1 day and 1 month). In addition, as expected for the 'no-shock controls' for which no tone-footshock association could be formed, no BOLD signal could be detected in the HIP for the 'trace>tone' contrast. Data were analyzed with SPM, as is the case in humans. Further segmentation of the HIP is necessary to establish whether CA3 is specifically disengaged over time when memories are (more) naturalistic. This study is one of a handful of studies investigating cognitive function with fMRI in awake rodents and shows that findings comparable to those obtained in humans can be achieved in rodents under similar experimental conditions.

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Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.10/RR6

Topic: H.08. Learning and Memory

Support: NIMH IRP

Title: Afferent connections to the septum and the hippocampus in the common marmoset.

Authors: *D. MATROV, K. CHRISTOPHER, I. INGRAM, Y. CHUDASAMA;
Section on Behavioral Neurosci., NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: The hippocampus (composed of the dentate gyrus, *Cornu Ammonis* (CA1-3) and the subiculum) and the septum are parts of the limbic system. Anatomical tracing studies conducted in the rat have shown that the hippocampus projects topographically and bilaterally upon the septal region, which in turn projects diffusely back to virtually the entire hippocampal formation (Risold and Swanson, 1997; Brain Res. Rev. 24:115-195). The hippocampus plays a crucial role in learning, memory, spatial navigation, and emotional processing. The septum seems to mediate contextual information provided by the hippocampus into decisions and actions. The close functional alignment of the two brain regions suggests overlapping connectivity with the rest of the brain, whereas divergent projections likely account for functional specialization of each region. Here, we approach this problem by examining the major anatomical afferents to the septum and the hippocampus in the common marmoset (*Callithrix jaccus*); a small New World primate with a complex social and vocal behavioral repertoire that is gaining popularity in neuroscientific research. Its lissencephalic cortex enables easy access for pathway-specific manipulation and low levels of aggressiveness make marmosets valuable species to study social and cooperative behavior. Of particular interest is the question of whether the prefrontal cortex projects directly to the hippocampus, of which there are some reports in rats and macaques. To study the afferent connectivity, we used primarily retrograde neuronal tracers Cholera toxin B conjugated to Alexa Fluor 488, 555, and 647, respectively (10% w/v dilution in saline), and Cascade Blue labeled dextran (1:1 mixture of 10,000 MW and 3,000 MW particles (1% w/v dilution in 0.1M phosphate buffer). Injection volumes were 500 nL into the septum and 400 nL into the hippocampus. Data from 5 injections in each the septum and the hippocampus will be quantified in our presentation. These data are collected from successful injections in 4 marmosets. On examination of the distribution of labeled cells, our preliminary data revealed that the septum receives input from prefrontal and temporal cortical regions, amygdala, midline thalamus, lateral hypothalamus, retrosplenial cortex and the hippocampus. Labeled cells after stereotaxic injections into the hippocampus were less extensive, observed in the entorhinal cortex, medial septal nucleus, the diagonal band of Broca, the anterior group of thalamic nuclei and the retrosplenial cortex. Presented results will be useful for planning of circuit-specific manipulations of neural pathways that involve the septum and hippocampus.

Disclosures: D. Matrov: None. **K. Christopher:** None. **I. Ingram:** None. **Y. Chudasama:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

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Program #/Poster #: PSTR109.11/RR7

Topic: H.08. Learning and Memory

Support: BRAIN Initiative NINDS R01 NS127128
the Whitehall Foundation

Title: Layer-specific properties of hippocampal CA1 functional cell types in freely-behaving macaques

Authors: *S. ABBASPOOR[1], K. L. HOFFMAN[2];
[1]Psychology, [2]Psychological Sci., Vanderbilt Univ., Nashville, TN

Abstract: The collective neural interactions of the hippocampal microcircuit form a critical component of an organism's ability to learn and remember. A mechanistic understanding of these neural interactions, including the canonical hippocampal oscillations, has relied on a detailed description of the constituent cell types of the microcircuit. Currently this description - and all associated biophysical models - derives almost entirely from mouse and rat data, whereas these cognitive functions are thought to generalize across mammalian species. Furthermore, some behavioral state-dependent oscillations differ between rodents and other orders, including primates. This begs the question of whether (or how) the constituent cell types in the hippocampus may differ in primates. We therefore sought to describe how unit activity statistics vary as a function of CA1 radial layer depth and of oscillation-defining behavioral states (e.g. awake, sleep). Two female macaques were chronically implanted with 2-4 depth-adjustable, 64/128 channel HD linear probes targeting the hippocampus and retrosplenial/cingulate and adjacent areas. Local field potentials (LFPs) and unit activity was collected as they learned a sequential item-in-context association task in a real 3D environment and during overnight sleep. The linear-array depth profile of sharp-wave ripples (SWRs) was used to identify different layers of CA1 and units were assigned a depth accordingly. Spiking statistics and depth of single units were used to group cell types, including, but not limited to putative pyramidal and fast-spiking inhibitory cells. Arousal/vigilance state affected the firing rates of all cell types, and changed the burst index of most cell types (total of 1291 units, $p < 0.05$, two-sided Wilcoxon signed rank test). Cell types differed in their SWR responses, including firing rate, participation probability, and proportion of units with phase locking (total of 1656 units, $p < 0.05$; Kruskal-Wallis test + Tukey's HSD). In contrast, median theta-band modulation index for all cell types was below 0, suggesting that no groups were strongly modulated by theta activity. Putative pyramidal cells split into superficial ($N = 287$) and deep ($N = 302$) groups showed differences in firing rate, burstiness, and SWR-firing probability ($p < 0.05$; 2-sided Wilcoxon rank sum). Our preliminary results suggest that functional cell types in monkey CA1 partially overlap with rodent types in their alignment to behavior-dependent LFP oscillations. Verification of homology across species will help to clarify common component processes and update biophysical models to account for species differences.

Disclosures: S. Abbaspoor: None. **K.L. Hoffman:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

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Program #/Poster #: PSTR109.12/RR8

Topic: H.08. Learning and Memory

Title: The primate hippocampus orthogonalizes codes for recognition memory and space along its longitudinal axis

Authors: *X. XU[1,2], K. DU[1], D. MAO[1];
[1]Ctr. for Excellence in Brain Sci. and Intelligence Technol. (Institute of Neuroscience), Shanghai, China; [2]Shanghai Tech. Univ., Shanghai, China

Abstract: The hippocampus is a critical structure involved in both memory and navigation. Previous research has primarily focused on investigating these functions separately, leading to an ongoing debate about the core role of the hippocampus. To address this issue, our study aimed to reconcile the involvement of the hippocampus in memory and navigation by examining how hippocampal neurons shift their representations during different tasks in macaque monkeys. We conducted two tasks: a recognition memory task and a free foraging task. In the recognition memory task, a significant proportion of hippocampal neurons showed rate modulation between viewing novel and repeat images. Strikingly, this rate modulation was positively correlated with memory performance - the fraction of time viewing novel images. Subsequently, we recorded the activity of the same hippocampal neurons as the monkeys freely explored an open arena for randomly scattered reward. Consistent with previous studies, we found that spatial view, rather than position, predominantly influenced the spatial selectivity of hippocampal neurons in macaques. Interestingly, the neurons that were selective for the memory task displayed minimal spatial tuning during free foraging, whereas the spatially tuned neurons exhibited limited memory-related activity. Furthermore, these largely separable codes for recognition memory and space were more prominent in the anterior and posterior regions of the hippocampus, respectively. Overall, our findings suggest the presence of an orthogonal long-axis gradient for recognition memory and spatial navigation within the hippocampus of macaque monkeys.

Disclosures: X. Xu: None. **K. Du:** None. **D. Mao:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.13/RR9

Topic: H.08. Learning and Memory

Title: An analysis of age-related human hippocampal microstructure and morphometry variance using non-negative matrix factorization

Authors: *T. AGYEKUM[1], C. L. GARCIA GARCIA[2], A. BUSSY[1], M. CHAKRAVARTY[3]; [1]Mcgill Univ., Montreal, QC, Canada; [2]McGill Univ. - IPN, Montreal, QC, Canada; [3]Biomed. Engin., Douglas Mental Hlth. Univ. Institute, McGill Univ., Verdun, QC, Canada

Abstract: Hippocampal atrophy has been shown to have significant implications in age-related cognitive variation. However, the degeneration of the hippocampus will likely occur across multiple dimensions; including overall morphology, myelin, and microstructural processes. Here, we use non-negative matrix factorization (NMF; a matrix factorization method that encourages sparsity and provides a parts-based representation) to study patterns of microstructural and morphological hippocampal variation using high-resolution magnetic resonance diffusion and structural imaging data(n=339; Human Connectome Ageing dataset). Fractional Anisotropy (FA), Mean Diffusivity (MD) and Jacobian determinants (JD) obtained from subjects' deformations to a common template are used as microstructural and morphological NMF voxel-wise inputs. We identified five microstructural and morphological components after stability analysis that demonstrate differential contributions of FA, MD, and JD. Linear models demonstrate subject-level weights are highly associated with age and sex. Left component 5 JD ($p = 0.00741$), right component 1 JD ($p = 0.0224$), and left 5 FA subject weights ($p = 0.0427$) predict verbal episodic memory, suggesting the predictive utility of our approach.

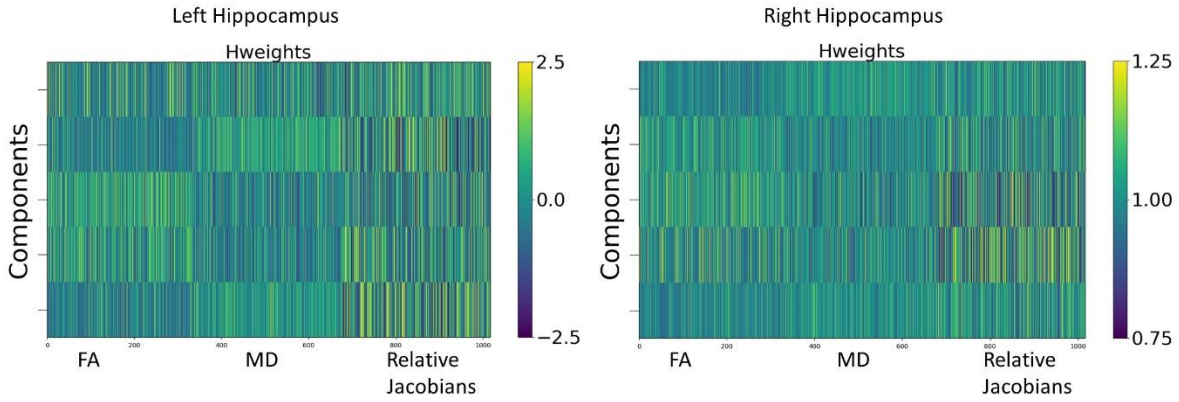

Figure 1 shows normalized weight matrices to visually see the microstructural and morphological features of each component in the study. As shown, each component, has different magnitudes for each metric. All raw scores of the metrics were normalized by z-scoring to make comparisons. The heat maps beside each image also helps to show the magnitude of the metrics in a particular component.

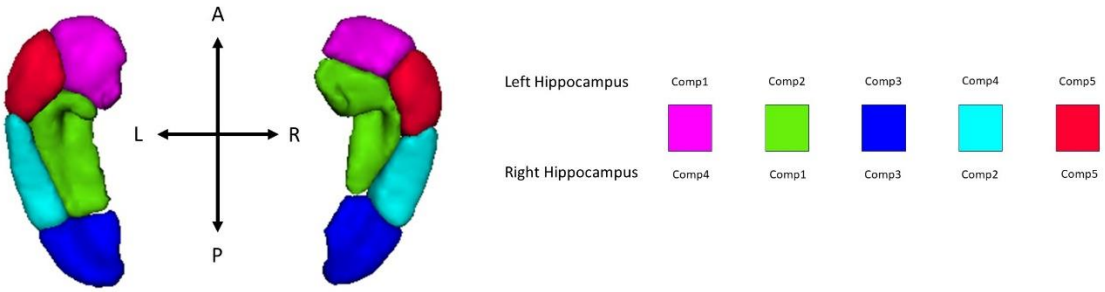

Figure 2 shows a 3-dimensional volumetric rendering of the left and right hippocampus after non-negative matrix factorization (NMF). The coloured regions show the asymmetric spatial regions that each of the five microstructural-morphological components (Comp), in each hemisphere, represent in stereotaxic space.

Disclosures: T. Agyekum: None. **C.L. Garcia Garcia:** None. **A. Bussy:** None. **M. Chakravarty:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

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Program #/Poster #: PSTR109.14/RR10

Topic: H.08. Learning and Memory

Support: National Key R&D Program of China 2019YFA0709502

Title: What and Where inputs to the human hippocampus for episodic memory revealed with magnetoencephalography

Authors: *E. ROLLS[1], G. DECO[2], Y. ZHANG[3], J. FENG[4];
[1]Computer Sci., Oxford Ctr. For Computat. Neurosci., Coventry, United Kingdom; [2]ETIC, Univ. Pompeu Fabra, Barcelona, Spain; [3]ISTBI, Fudan Univ., Shanghai, China; [4]Computer Sci., Warwick Univ., Coventry, United Kingdom

Abstract: The hierarchical organisation between 25 ventral stream visual cortical regions and 180 cortical regions was measured with magnetoencephalography using the HCP-MMP1 atlas in 83 Human Connectome Project participants performing a visual memory task. The aim was to reveal the hierarchical organisation using a whole-brain model based on generative effective connectivity computed using time delays of 20 ms with this fast neuroimaging method.

In a ventromedial visual stream, V1-V4 connect to ventromedial regions VMV1-3 and VVC. VMV1-3 and VVC connect to the medial parahippocampal gyrus PHA1-3, which, with the VMV regions, include the parahippocampal scene area. The medial parahippocampal PHA1-3 regions have connectivity to the hippocampal system regions the perirhinal cortex, entorhinal cortex, and hippocampus. This provides a 'where' input to the human hippocampus with spatial view cells built from ventral visual stream feature analysis, not from what has been assumed, the parietal cortex. The parietal cortex inputs to this ventromedial system may contribute to idiothetic (self-motion) update of spatial view cells, allowing update of scene representations that are invariant with respect to eye position, head direction, and facing direction.
In a ventrolateral visual pathway V1-V4 (especially V4) have effective connectivity with V8, the fusiform face cortex FFC, and the posterior inferior temporal cortex PIT. These regions in turn have effective connectivity to inferior temporal cortex visual regions TE2p and TE1p. TE2p and TE1p then have connectivity to anterior temporal lobe regions TE1a, TE1m, TE2a, and TGv, which are multimodal. The ventrolateral ventral visual stream regions have input to the human hippocampus in part via lateral parahippocampal cortex region TF, introducing 'what' information about faces and objects to the human hippocampus for episodic memory.
These discoveries help to provide a foundation for understanding the functioning of the hippocampus in memory in humans and other primates.
References available at https://www.oxcns.org
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Rolls, E. T. (2023) Hippocampal spatial view cells for memory and navigation, and their underlying connectivity in humans. Hippocampus 33: 533-572.
Rolls, E. T. (2023) Hippocampal spatial view cells, place cells, and concept cells: view representations. Hippocampus 33: 667-687.
Rolls, E. T., Deco,G., Huang,C-C. and Feng,J. (2023) Multiple cortical visual streams in humans. Cerebral Cortex 33: 3319-3349.

Disclosures: **E. Rolls:** None. **G. Deco:** None. **Y. Zhang:** None. **J. Feng:** None.

Poster

PSTR109. Hippocampal Formation Circuitry II

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR109.15/RR11

Topic: H.08. Learning and Memory

Support: Canadian Institutes of Health Research (CIHR) operating grant (MOP180400)
CIHR Mid-Career Investigator Prize in Research in Aging (MOP179758)

Title: Contributions of hippocampal subregions, cellular subfields, and encoding strategies to the age-related verbal memory performance across the adult lifespan

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Abstract: In this study, we aimed to understand the contributions of anteroposterior hippocampal subregions (head, body, tail), hippocampal subfields (cornu ammonis 1-3, dentate gyrus, and subiculum), and encoding strategies to the age-related verbal memory decline. Healthy participants (n=122, aged 18-85) were administered the California Verbal Learning Test-II to evaluate verbal episodic memory performance and encoding strategies (semantic and subjective clustering). Participants underwent 4.7T Magnetic Resonance Imaging (MRI) brain scan with subsequent hippocampal subregions and subfields manual segmentation. Structural equation modeling was used to test the relationship between age, hippocampal volumes, encoding strategies, and verbal memory performance. Age was negatively associated with verbal memory performance in both males (r = -.519, p < .001) and females (r = -.341, p = .005). Increased age was also found to be linked with lower subjective clustering strategy (r = -.222, p =. 014), but not with semantic clustering (r = -.076, p = .406). Adjusting for the effects of age, better verbal memory performance was related to both higher semantic (r = .562, p < .001) and subjective clustering strategies (r = .463, p < .001). While total hippocampal volume was not associated with verbal memory performance after accounting for the effects of semantic clustering or subjective clustering, we found the volumes of posterior hippocampus (body; p = .016) and subiculum (p = .014) showed significant effects on verbal memory performance. Additionally, the age-related volume decline in hippocampal body volume contributed to lower use of semantic clustering (p = .014), resulting in lower verbal memory performance. Our results showed that posterior dentate gyrus and cornu ammonis 1-3 subfields supported verbal memory through encoding strategies while the subiculum exerted direct effect on verbal memory performance, suggesting its role in memory retrieval rather than encoding. These findings highlight the significance of examining both anteroposterior axis of the hippocampus and its cellular subfields underlying episodic memory function in the process of normal aging.

Disclosures: K. Hoang: None. **Y. Huang:** None. **E. Fujiwara:** None. **N. Malykhin:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.01/RR12

Topic: H.08. Learning and Memory

Support: Royal Society 175918
Wellcome Trust Senior Research Fellowship, 220886/Z/20/Z
Royal Society University Research Fellowship, UF150692
ERC consolidator DEVMEM

Title: The development of memory specificity in the postnatal rat hippocampus

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Abstract: Episodic memory, or memory for events, is a characteristic that emerges late in humans. Prior to developing episodic memory, individuals experience infantile generalization, involving impaired memory recall and positioning of specific events within their spatial-temporal framework (Nelson and Gruendel, 1981). One proposed explanation is a disruption in the balance between pattern separation and pattern completion, the mechanisms by which the brain reduces the overlap between neural representations with contextual overlap, to produce separate memories and retrieves memories from incomplete sensory information. In development, an inability to separate similar memories and an over association of sensory information could lead to a bias of generalization over specificity (Keresztes et al., 2018; Ramsaran et al., 2019). A prevailing theory suggests that in adults pattern separation and pattern completion occur in the dentate gyrus (DG) and CA3 regions sub-regions of the hippocampus respectively (Marr, 1971). In addition, the hippocampal subfield CA3 has also been implicated in pattern separation (Goodsmith et al., 2019). Therefore the immaturity of this brain region in development could be causally linked to infantile generalization, in particular, the late maturation of DG granule cells. Traditionally, in in vivo electrophysiological studies, it has been a challenge to distinguish between the two main excitatory cell types of the DG: granule and mossy cells. Despite granule cells being the main excitatory cells in the DG, they exhibit sparse firing patterns. Additionally, mossy cells, although less abundant, have higher firing rates and can be recorded at greater distances. Here we address this issue by analyzing cells within the developing DG-CA3 circuit, utilizing their firing properties and anatomical positioning to differentiate between mossy cells, granule cells, and CA3 pyramidal cells (Goodsmith et al., 2019; Senzai and Buszaki, 2017). Using tetrodes and silicon probes, we evaluated the pattern separation ability of these cells in 16 rats exposed to varied spatial contexts, assessing their encoding capability for memories with similar or distinct contextual elements across the onset of hippocampal memory (P16-P32). Preliminary outcomes demonstrate an impairment in the ability to perform pattern separation based on firing rate in young animals for granule cells but not mossy cells. The data presented here elucidates the changing properties of various cell types within the dentate gyrus-CA3 circuit, thereby contributing to a deeper understanding of their role in the emergence of pattern separation during the postnatal period in rats.

Disclosures: I. Varsavsky: None. **I. Varsavsky:** None. **F. Cacucci:** None. **T.J. Wills:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.02/RR13

Topic: H.08. Learning and Memory

Support: NIH Grant R35 NS127219

Title: Theta burst stimulation of the perforant path differentially potentiates a sparse population of dentate gyrus granule cells

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Abstract: Granule cells (GCs) of the dentate gyrus (DG) are the primary excitatory target of the perforant path (PP) inputs from the entorhinal cortex. The hippocampal formation is essential for episodic and spatial memory, and the DG is thought to act as its gatekeeper. Bliss and Lomo first demonstrated long-term potentiation (LTP) in the rabbit DG after high frequency stimulation of the PP. In subsequent experiments, theta burst stimulation (TBS) has become the standard protocol for LTP induction. Although GC LTP has been studied extensively, many questions remain about GC heterogeneity and the impact of LTP on function at the circuit level. Episodic and spatial memories are thought to be encoded in ensembles of coactivated cells. Understanding the ways in which cells are coactivated and copotentiated is essential to understanding the formation of complex memories. To address these questions, we employed a hybrid optical voltage sensor (hVoS 1.5) to record voltage changes from multiple GCs simultaneously. We used neonatal Prox1 expression to target GCs via Cre recombinase. Sections of coronal hippocampus prepared from adult male and female mice contained multiple probe-expressing mature GCs. Optical voltage recordings were obtained at 29°C-32°C enabling us to image voltage changes in 9 to 20 GCs within a slice. TBS stimulation of the middle molecular layer induced LTP in nearly half of hVoS-labeled GCs. Notably, potentiation was not uniform across GC soma and dendrites, and dendritic responses were differentially potentiated across the molecular layer. These experiments showed a higher incidence of double spikes with ~ 5 msec intervals following LTP induction. In summary, our findings may indicate that DG GCs are not uniform but heterogeneous in their expression of LTP. These findings have implications for the locations of potentiated synapses and the computational role of LTP in DG memory encoding.

Disclosures: C.A. Rossmeissl: None. **M.B. Jackson:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.03/RR14

Topic: H.08. Learning and Memory

Title: Transgenic Access Enables Structural and Functional Characterization of Semilunar Granule Cells of the Mouse Dentate Gyrus

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Abstract: The hippocampus plays a critical role in learning and memory formation. The trisynaptic circuit of the hippocampus is comprised of three excitatory synapses: Entorhinal cortex (EC) to dentate gyrus (DG), DG to CA3, and CA3 to CA1s. The DG, conceptualized as a gateway to the circuit, plays a leading role in filtering incoming cortical information via brief responses in granule cells (GC). Brief responses of GC are thought to be critical for encoding memories while alteration is linked to memory impairment and epileptogenesis. A rare subtype of GC, semilunar granule cells (SGCs), enriched near the boundary of the dentate molecular layer, exhibit distinct morphology and physiology that are thought to constrain DG GC activity. In response to EC input, SGCs undergo prolonged firing, and through the recruitment of interneurons, broadly and durably inhibit GC. Previously reported characterization of rodent SGCs is largely based on visually guided patch clamp recordings from acute brain slices. Therefor experimental manipulation and validation of SGCs function has been hampered by a lack of specific access in experimental animal models. To address this gap, we pursued two independent transgenic strategies towards specific and efficacious access to SGCs of the mouse. In one strategy, GFP expression under Kit receptor tyrosine kinase promoter in a BAC based transgenic line Kit-eGFP generated via Gensat (RRID: MMRRC 030363-UCD), labelled semilunar cells of DG, but outside of the DG, this transgene labeled multiple other cell types. We therefore devised a viral based intersectional strategy to functionalize Kit GFP expressing SGCs with Flp recombinase. In a second independent strategy, we screened the Allen Brain Atlas recombinase characterization resources for patterns matching the distribution of SGCs. One candidate line was 25463 Rdav 2A Cre ERT2, an enhancer trap line expressing inducible Cre which we crossed to the Cre reporter (tdTomato) line. For both strategies, we validated the specificity in SGCs by microscopy (distribution and dendritic span) and electrophysiology (input resistance and persistent firing) in the mouse brain. Our electrophysiological results confirm that an overwhelming majority of labelled cells exhibit input resistance and persistent firing properties like SGCs, thus providing evidence of reliable genetic labelling of distinct cell type of DG. Following further ex vivo optimization and validation, we anticipate that these strategies will empower the field to assess the physiology and role of SGCs in vivo, both in typical development and learning, as well as in models for human disease.

Disclosures: **T. Zaman:** None. **D. Rexford:** None. **A. Stafford:** None. **D. Vogt:** None. **M. Williams:** None.

Poster

PSTR110. Dentate Gyrus

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Program #/Poster #: PSTR110.04/RR15

Topic: B.08. Epilepsy

Support: 1F31NS124290-01
R01NS097750
R01NS069861

Title: Differential Glutamatergic Drive to Dentate Semilunar Granule Cells and Granule Cells: Implications for Refinement of Memory Engrams in Healthy and Epileptic Circuits

Authors: *L. DOVEK[1], A.-T. NGUYEN[2], V. SANTHAKUMAR[3];
[1]Univ. of California, Riverside Biomed. Sci. Grad. Program, Riverside, CA; [3]Mol. Cell and Systems Biol., [2]Univ. of California, Riverside, Riverside, CA

Abstract: The hippocampal dentate gyrus (DG) plays a major role in episodic memory formation by processing dense cortical inputs into sparse granule cell (GC) activity. Semilunar granule cells (SGCs), a subtype of DG projection neurons with expansive molecular layer dendritic arbors and persistent firing, have been proposed to shape memory processing by supporting feedback inhibition of GCs (Larimer et al., 2010). SGCs differ from GCs in their intrinsic physiology and are recruited in memory ensembles (engrams). However, how they regulate DG circuit dynamics and memory formation is not fully understood. This is crucial in the context of temporal lobe epilepsy, as epileptogenesis leads to changes in the DG circuit and impairs memory formation. Here we evaluated the recruitment of SGCs to DG memory engrams during encoding and recall and tested whether cell-type specific differences in excitatory inputs could drive preferential SGC recruitment to engrams. We further examined if cell specific input differences could contribute to the breakdown of engram formation in a model of experimental epilepsy .To assess neuronal recruitment to engrams, cFOS TRAP-tDT mice, trained on a Barnes Maze spatial memory task were induced to express tdT in neurons activate on day 6 of training. Following a reacquisition trial a week later, mice were sacrificed for immunostaining for cFOS. The proportional recruitment of SGCs among tDT labeled cells in trained mice exceeded their relative abundance of about 5% of DG GCs. More tdT labeled cells colocalized with cFOS expression following the reacquisition trial, consistent with engram reactivation. In whole cell recordings from *ex vivo* slices, SGCs, identified by posthoc morphology of biocytin fills, received more frequent spontaneous excitatory postsynaptic currents (sEPSCs) than GCs. Recordings of mice with AAV driven channelrhodopsin expression in medial or lateral entorhinal cortex or hilar mossy cells identified layer specific differences in excitatory inputs to SGCs and GCs. Correspondingly, there were layer-specific differences in dendritic spine density between cell types. Whole cell recordings from GCs and SGCs in slices from mice 1 month after pilocarpine induced status epilepticus (SE) identified increases in sEPSC frequency in both cell types, compared to age-matched saline-injected controls. SGCs, but not GCs, showed a reduction in perforant path evoked EPSC amplitude after SE.Our data suggest that cell specific differences in excitatory inputs could underlie preferential SGC recruitment to memory engrams. Changes in excitatory inputs to SGC after SE likely undermines their role in memory processing in epilepsy.

Disclosures: L. Dovek: None. **A. Nguyen:** None. **V. Santhakumar:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

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Program #/Poster #: PSTR110.05/RR16

Topic: H.08. Learning and Memory

Support: The Wellcome Trust SJ1197, WT084585
China Scholarship Council and University of Bristol U135572-105
EPSRC DTP studentship (ref. 2407565).

Title: Indirect feedback inhibition from hilar mossy cells enhances the sparse activation of dentate granule cells and frequency-dependent pattern separation

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Abstract: The discrimination of similar episodes and places and their representation as distinct memories depend on a process called pattern separation that is performed by the circuitry of the hippocampal dentate gyrus (hDG). Excitatory hilar mossy cells (MCs) support pattern separation through their connections with different inhibitory interneuron (INT) populations that provide feedback inhibition to granule cells (GCs). In this study, we investigated how MCs and their synaptic connections with cholecystokinin-expressing interneurons (CCKIs) and parvalbumin-expressing interneurons (PVIs) influence the dynamics of hDG circuitry by using pharmacological agents to reduce neurotransmission from MCs or different INTs, genetically modified (GM) mice to selectively remove MCs from hDG circuitry and optogenetics to manipulate INT activity during GC whole cell/field recordings (age 8-10 weeks, n=5-18 animals/group). In addition, we used computational models to simulate hDG circuit dynamics. Our results showed that the net influence of MCs on GC activity is frequency-dependent and inhibitory, likely through the recruitment of INTs, since (i) GC responses to 20Hz and 50Hz stimulation of the medial perforant pathway (MPP) were less depressed in GM mice (that lacked MCs) compared with WT, but not at 5Hz; (ii) GC responses to 20Hz and 50Hz stimulations of the MPP were less depressed in the presence of GABAA receptor antagonist picrotoxin (PTX) in WT animals but not to 5Hz; (iii) GC responses to 20Hz and 50Hz stimulation of the MPP were less depressed, compared to controls, by pharmacologically reducing (40.9%±2.2%) MC-GC synaptic transmission with the type 1 cannabinoid receptor agonist WIN55,212-2 (WIN). Secondly, our preliminary results confirmed that CCKIs and PVIs provide feedback inhibition of GCs at different stimulation frequencies: (i) GC responses to 10Hz and 20Hz stimulation of the MPP were increased by blocking CCKI-GC synaptic transmission using the N-type voltage-gated calcium channel inhibitor ω-Conotoxin GVIA in WT hippocampal slices; (ii) GC responses to 5Hz and 10Hz stimulation of the MPP were restored by activating ChR2-expressing PVIs in GM animals. Finally, our computational model showed that the removal of MCs from DG circuitry led to the disinhibition of GC activity through their indirect MC-basket cell-GC connections. Together, these findings suggest that the net inhibitory influence of MCs on GC activity is frequency-dependent due to the recruitment of CCKIs and PVIs at different stimulation frequencies.

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Poster

PSTR110. Dentate Gyrus

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Program #/Poster #: PSTR110.06/RR17

Topic: H.08. Learning and Memory

Support: Alana Down Syndrome Center

Title: The Impact of Gamma Sensory Stimulation in Adult Ts65Dn

Authors: *B. SCHATZ, B. L. JACKSON, M. ISLAM, D. PARK, L.-H. TSAI;
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Abstract: Gamma Entrainment Using Sensory Stimulus (GENUS) at 40Hz has previously been shown to attenuate Alzheimer's disease (AD) pathology such as amyloid and tau levels, as well as improved behavioral testing performance in mouse models of AD. Trisomy 21 shares a multitude of cognitive and biological phenotypes with AD, especially within the hippocampal circuit. We investigated the effects of chronic exposure to GENUS in adult Ts65DN mice, a model of Down syndrome (DS). Mice were exposed to one hour of auditory and visual (A+V) GENUS (ST group) or one hour of ambient light and sound as a no stimulus control (NS group) daily for three weeks. Following three weeks of chronic GENUS exposure, ST mice showed a significant improvement in recognition index during novel object location and novel object recognition compared to NS mice, as well as an improvement in spontaneous alternation, a measure of spatial working memory. The animals were perfused, and their hippocampi collected. Single nuclei RNA sequencing of the hippocampi revealed notable transcriptomic changes following chronic GENUS exposure, particularly in the excitatory neurons. Genes related to synaptic functions were significantly upregulated in ST mice. To validate the RNAseq data, brain slices were stained for presynaptic and postsynaptic markers, and the colocalization of these markers was used as a proxy for mature functional synapses. Interestingly, ST mice showed a significant increase in synapse number within the dentate gyrus (DG) compared to NS mice. However, the CA1 region of the hippocampus showed no significant synaptic differences between groups, potentially suggesting a region-specific effect of GENUS. Further analyses of the single nuclei data suggested GENUS-related increased adult neurogenesis in DG, which was subsequently experimentally validated. These data suggest that GENUS can ameliorate cognitive impairment in Ts65Dn mice through modulation of synaptic organization as well as increased neurogenesis and may have potential as a therapeutic approach to boost cognitive performance in individuals with Down Syndrome.

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Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.07/RR18

Topic: H.08. Learning and Memory

Support: NFR Grant 276047

Title: Cholecystokinin-expressing interneurons as intermediaries of noradrenergic suppression of hippocampal granule cells

Authors: *I. GLOVACI, K. VERVAEKE, H. HU;
Fac. of Medicine, Inst. of Basic Med. Sci., Univ. of Oslo, Oslo, Norway

Abstract: Pattern separation in the dentate gyrus plays a key role in decorrelating inputs from the entorhinal cortex during episodic memory formation. A key mechanism underlying this function is the sparseness of dentate granule cell activity, which facilitates the segregation of memory representations within the coding space. Dentate gyrus neuronal activity, which is tightly regulated by several neuromodulatory systems, displays strong behavioral state dependence. For example, previous in vivo studies demonstrate a reduction of action potential rate in granule cells during a state of arousal and during novelty detection tasks. Here, we have determined how the locus coeruleus noradrenergic system, implicated in both arousal and attention, modulates dentate gyrus granule cell activity. By performing patch-clamp recordings in acute brain slices from mice, we demonstrate that optogenetic activation of noradrenergic axons inhibits action potentials in single granule cells evoked by stimulation of the perforant path. At the population level, optical and electrophysiological recordings indicate that noradrenaline (NA) decreases the size of active granule cell ensembles in response to inputs from the entorhinal cortex. This optogenetic suppression of granule cell activity is occluded by noradrenergic receptor blockers, but insensitive to dopaminergic receptor blockers, while being mimicked by bath application of noradrenaline. These pharmacological analyses provide strong evidence to support that the suppression of granule cells, evoked by optogenetic activation of noradrenergic axons, does not require the co-release of dopamine from noradrenergic fibers. Moreover, our experiments indicate that the noradrenergic suppression of granule cell activity depends on the enhancement of a feedforward synaptic inhibition component mediated by cholecystokinin-expression interneurons (CCK^+ INs). This idea is reinforced by targeted recordings from individual CCK^+ INs, demonstrating that NA facilitates the synaptic activation of CCK^+ INs. In sharp contrast, synaptic recruitment of parvalbumin-expressing interneurons by perforant path axons is suppressed by NA. Taken together, these experiments have identified CCK^+ INs as key intermediaries between noradrenaline release in the dentate gyrus and the subsequent inhibition of granule cell activity. As such, our results may provide important insights into how different interneuron types contribute to pattern separation in the dentate gyrus in a behavioral state-dependent manner, and may elucidate the mechanisms underlying the reduction of granule cell activity during novelty detection and arousal.

Disclosures: I. Glovaci: None. **K. Vervaeke:** None. **H. Hu:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.08/RR19

Topic: H.08. Learning and Memory

Support: 1RF1AG062166

Title: Adiponectin AdipoR2 receptors in the dentate gyrus regulate cognitive behavior.

Authors: *M. MALEK, Y. LEI, J. GARZA, X.-Y. LU;
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Abstract: Despite some evidence of involving AdipoR1 signaling in cognitive functions, the role of AdipoR2 and its specific pathway is less clear. Here, we investigated the possible role of hippocampal AdipoR2 receptors in mediating cognitive functions and possible molecular mechanisms. AAV-Cre was bilaterally injected into the dentate gyrus (DG) to induce DG-specific AdipoR2 knockdown. The mice with DG-specific AdipoR2 knockdown showed impaired cognitive behaviors in the novel object recognition and Y-maze spontaneous alternation tests, while their locomotor activity and anxiety levels remained normal. To further investigate the relationship between AdipoR2 and its downstream signaling pathway, we examined the colocalization of AdipoR2 with PPARα in DG neurons using AdipoR2 reporter mice. Our results indicated that the majority of AdipoR2-expressing neurons contained PPARα in the DG. To determine if the cognitive effects of AdipoR2 were mediated through PPARα signaling, we achieved DG-specific PPARα knockdown by injecting AAV-Cre into the DG of PPARα $^{flox/flox}$ mice. Surprisingly, mice with DG-specific PPARα knockdown showed normal cognitive behaviors, suggesting that PPARα is not involved in mediating the cognitive effects of AdipoR2 in the DG. To further investigate the specific role of PPARα in AdipoR2-expressing neurons, we generated mice with conditional knockout of PPARα specifically in AdipoR2-expressing neurons. These mice did not display any cognitive phenotypes but exhibited increased locomotor activity, indicating that PPARα in these neurons may be involved in regulating locomotion rather than cognitive functions. In conclusion, these findings highlight the critical role of AdipoR2 in the DG for cognitive functions. However, our results suggest that the cognitive effects of AdipoR2 are mediated through signaling pathways other than PPARα. Further research is needed to identify specific pathways downstream of AdipoR2 actions in cognitive behaviors.

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Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.09/RR20

Topic: H.08. Learning and Memory

Support: National Taiwan University, College of Medicine (112L895401)

Title: Investigate the memory-enhancing effect and neurostructural alterations of dietary restriction-derived probiotic

Authors: *C.-C. HUANG[1,2,3], Y.-C. LIU[2], P.-Y. WANG[2];
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Abstract: Dietary restriction (DR), which refers to consuming 20% to 40% of daily food intake while maintaining adequate nutrition, is one of the most renowned diet regimens for prolonging lifespan and improving healthspan, particularly in the fields of metabolic health and cognitive function. Mechanistically, DR improves proteostasis, regulates inflammation, modulate intracellular signaling, and maintain glycemic profile to achieve beneficial effects. Given the extreme challenge to maintain such a rigid regimen in our daily life, it is crucial to pinpoint suitable downstream effectors and develop strategies to recapitulate the beneficial effect of DR. Recently, the gut microbiota, the collective of commensal bacteria residing in our gut, has emerged as an important factor that shapes a wide range of biological functions. Various beneficial effects of DR, including metabolic health and inflammation, have been proven to be mediated by the alteration of the gut microbiota. Accordingly, we hypothesized that DR-derived gut microbiota mediates the memory-enhancing effect of DR. Antibiotics-treated mice and germ-free mice were used as loss-of-function models to examine the necessity of the gut microbiota in DR-induced memory enhancement. Consistent to our hypothesis, DR-induced memory enhancement was diminished in the absence of the gut microbiota assayed by multiple memory behavior tasks including object memory and social memory. Accompanied with memory enhancement, DR also induces neurostructural alterations such as increased spine density, reduced dendritic complexity, and enhanced adult hippocampal neurogenesis. These effects were abolished in both antibiotics-treated mice and germ-free mice. Furthermore, mice with normal food intake (*ad libitum*, AL) but receive fecal microbiota transplantation from DR (FMT-DR) would recapitulate aforementioned benefits. Via 16S metagenomic sequencing, we have identified several commonly enriched in memory-enhanced DR and FMT-DR mice. In the following study, we will test these presumed probiotics for their memory-enhancing effects. We will utilize metabolomics and transcriptomics approaches to uncover the underlying bacteria-host interactions, including the production of bacteria-associated metabolites and the host's molecular response, which contribute to improved memory.We believed this study would provide a comprehensive understanding of how DR-derived gut microbiota elicit beneficial effects, providing a solid backbone to identify a druggable target to recapitulate DR-associated benefits and ameliorate diseases.

Disclosures: C. Huang: None. **Y. Liu:** None. **P. Wang:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.10/SS1

Topic: H.08. Learning and Memory

Support: R01ActNS064025Project14Year
R01ActNS105438Project05Year

Title: Adult born neurons excel at pattern separation computation

Authors: *H. PANIKKAVEETTIL ASHRAF, J. RYU, K. NATHAN, J. I. WADICHE, L. S. OVERSTREET-WADICHE;
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Abstract: The hippocampal circuit stores and recalls neuronal activity patterns to encode experiences and form episodic memories. Discriminating between similar memories requires pattern separation, which transforms similar patterns of incoming neural activity into divergent output patterns. The dentate gyrus; a hippocampal region with continuous adult neurogenesis, mediates pattern separation to increase memory capacity and prevent overlap of pattern recall in downstream CA3. Selective manipulation of neurogenesis suggests young, adult-born granule cells (abGCs) play a crucial role in dentate pattern separation. However, a paradoxical feature of abGCs is high excitability, which predicts that they act as integrators that degrade pattern separation. A real-time assessment of pattern decorrelation of input spike trains by young abGCs is lacking, hence obscuring their computational capacity relative to mature GCs. In this study, we used simultaneous whole-cell recording of abGCs and mature granule cells (mGCs) to assess real-time changes in output spike patterns by opto-genetically driving predefined input spike trains with different degrees of similarity. Our results indicate that abGCs perform a more substantial pattern decorrelation than mGCs, resolving an apparent paradox of how highly excitable cells can promote pattern separation. The degree of perforant path synaptic connectivity correlates with pattern separation, suggesting that low synaptic connectivity generates the computational advantage of abGCs. Together these results suggest that limited innervation of abGCs by cortical axons enhances pattern decorrelation of input spike trains, potentially contributing to the role of adult neurogenesis in memory resolution.

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Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

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Program #/Poster #: PSTR110.11/SS2

Topic: H.08. Learning and Memory

Support: 1R56AG072473
1RF1AG079269

Title: A novel enhancer-AAV approach to selectively target dentate granule cells

Authors: ***E. BANKS**[1], C.-A. N. GUTEKUNST[2], G. VARGISH[3], K. PELKEY[4], A. EATON[5], C. J. MCBAIN[6], J. Q. ZHENG[7], V. OLAH[8], M. J. ROWAN[1];
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Abstract: The mammalian brain contains the most diverse array of cell types of any organ, including dozens of neuronal subtypes with distinct anatomical and functional characteristics. Through use of Cre lines, access to specific neuron types has steadily improved over past decades. Despite their extensive utility, development and cross-breeding of Cre lines is time-consuming and expensive, presenting a significant barrier to entry for many investigators. Further, cell-based therapeutics developed in Cre mice are not directly translatable. To overcome these limitations, several viral (AAV) vectors utilizing neuron-type-specific regulatory transcriptional sequences (enhancer-AAVs) were recently developed to target specific excitatory neuron types in the cortex. However, enhancer-AAV tools for selective targeting of distinct excitatory populations in hippocampus remain uncharacterized. Using a publicly available RNAseq dataset, we evaluated the potential of several recently identified enhancer sequences for excitatory neuron targeting in hippocampus. Here we evaluated an enhancer with predicted selectivity for dentate gyrus (DG) granule cells. YFP expression driven via this enhancer was observed in the DG-CA3 region following stereotactic injection of adult C57BL/6J mice. We found that this AAV selectively labeled granule cells and their mossy fiber axons in CA3, but not other nearby excitatory cells (i.e., CA3 pyramidal cells and hilar mossy cells), despite their proximity to the DG. As the DG is likely a locus for seizure generation, incorporating functional constructs (e.g., opsins, DREADDs) into this enhancer-AAV to manipulate DG granule cell activity may be a promising area for future preclinical research. In summary, this enhancer-AAV approach should allow for rapid genetic modulation of DG granule cells across mouse models and potentially other species.

Disclosures: E. Banks: None. **C.N. Gutekunst:** None. **G. Vargish:** None. **K. Pelkey:** None. **A. Eaton:** None. **C.J. McBain:** None. **J.Q. Zheng:** None. **V. Olah:** None. **M.J. Rowan:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.12/SS3

Topic: H.08. Learning and Memory

Support: DFG BA1582/12-1
FOR2143
HA 8939/1-1
EMBO ALTF 6-2019
ERC-AdG 787450

Title: Subfield-specific interneuron circuits govern the hippocampal response to novelty

Authors: *A. CAZALA[1], T. HAINMUELLER[2], M. BARTOS[1];
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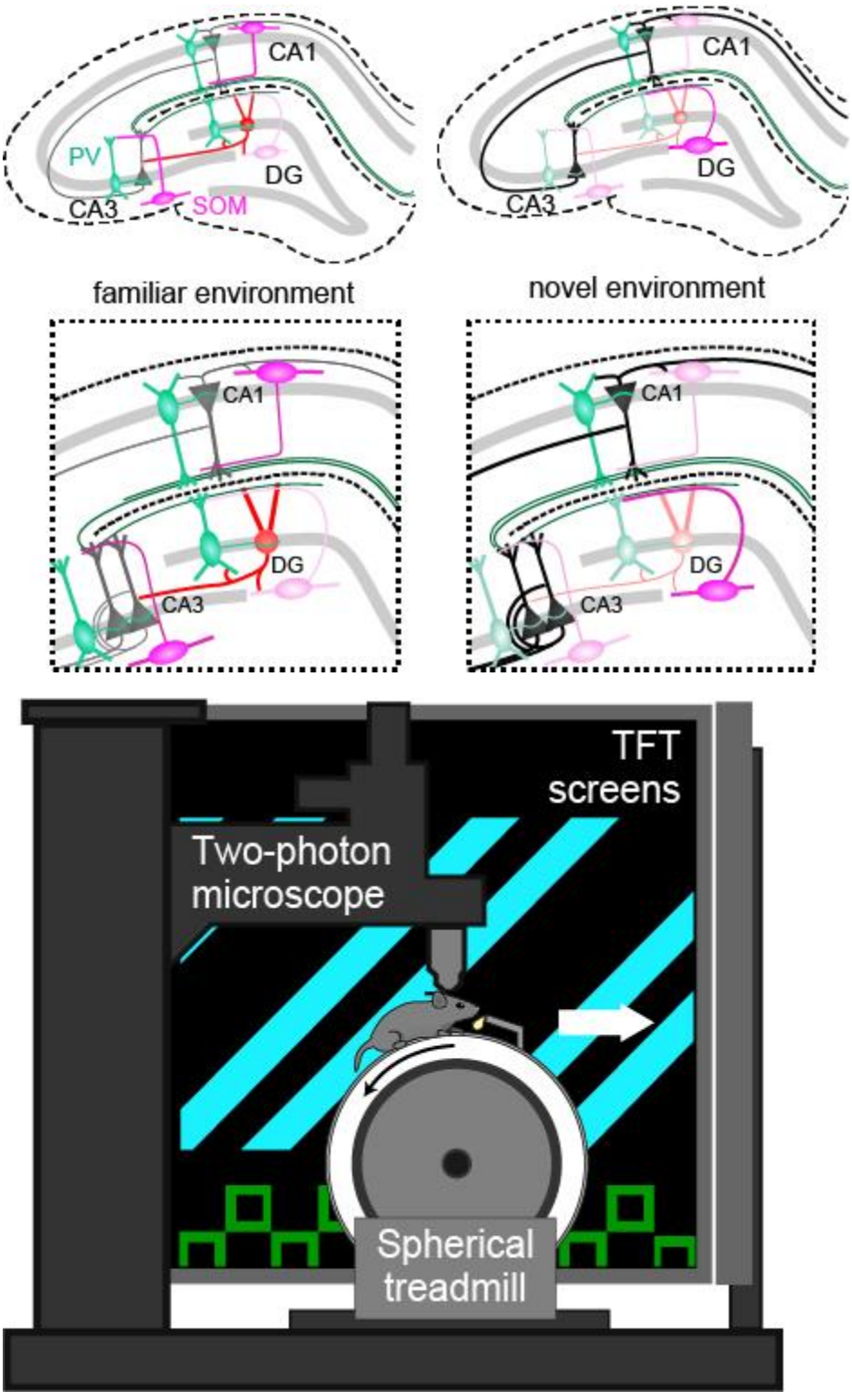
Abstract: The hippocampus is the brain's center for episodic memories and is critical for spatial navigation and novelty-detection, among others. Its subregions, the dentate gyrus (DG), CA2/3, and 1, are involved in these functions in distinct ways. DG is crucial for discriminating novel contents from similar familiar ones while CA3 aids fast encoding of novel information. Hippocampal principal cells (PC) represent episodic features like movement, space, and context but little is known about GABAergic interneurons (IN) and how they influence on PCs activity and contribute to hippocampal function. Here, we performed two-photon calcium imaging of parvalbumin (PV)- and somatostatin (SOM)-expressing INs in the DG and CA1-3 of mice exploring virtual environments. PV-INs throughout the hippocampus increased activity with running-speed and reduced it in novel environments. SOM-INs displayed a dichotomy: CA1-3 SOM-INs behaved similar to PV-INs, but their DG counterparts increased activity during immobility and in novel environments. Congruently, chemogenetic silencing of DG SOM-INs caused increased activation of DG granule cells (GC) in novel environments and decreased context selectivity, while silencing of DG PV-INs had opposite effects. Our data indicate unique roles for DG PV- and SOM-INs that are distinct from their CA1-3 counterparts and may support novelty-dependent, dynamic routing of information through the hippocampus.



Disclosures: **A. Cazala:** None. **T. Hainmueller:** None. **M. Bartos:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.13/SS4

Topic: H.08. Learning and Memory

Support: euSNN-106017801

Title: Morphological and functional characteristics of NDNF-expressing interneurons in the dentate gyrus

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Abstract: The Dentate Gyrus (DG) receives rich multimodal inputs from the entorhinal cortex through the perforant path, and it translates them into a sparse code for the CA3. During the exploration of new environments, groups of DG granule cells (GCs) become active and contribute to the formation of new memories. The activity of GCs is strongly modulated by a large network of inhibitory interneurons (INs) which allow the sparsification and orthogonalization of the DG code. However, a clear understanding of how the different INs types contribute to DG function during memory formation is still missing. Recently, a novel population of GABAergic INs expressing the *Neuron-Derived Neutrophic Factor* (NDNFIs) has been identified as a key component in the modulation of cortical networks. We found that NDNFIs are also integral part of the DG network, where they provide distal dendritic inhibition to GCs. We investigated their distribution, morphology, electrophysiological properties, and functional connectivity. We distinguished 2 subpopulations of NDNFIs in the DG based on their soma location: molecular layer NDNFIs (ML-NDNFIs), that include the neurogliaform cells, and hilar NDNFIs (hNDNFIs), mainly located in the subgranular zone of the DG. Although they express similar molecular markers, ML-NDNFIs and hNDNFIs show different morphological and electrophysiological characteristics. In accordance with their dendrite's distribution, ML-NDNFIs and hNDNFIs receive synaptic inputs prevalently from the perforant path and mossy fibers' collaterals, respectively. Thus, we propose they differently contribute to feedforward and feedback control of GCs. Using in-vivo 2-photon calcium imaging and pharmacological modulation of NDNFIs we are currently investigating the contribution of NDNF-expressing interneurons to the DG function. Combining ex-vivo and in-vivo approaches, we will provide the first functional characterization of DG NDNFIs, and we will investigate their contribution to DG network dynamics and memory formation.

Disclosures: F. Torelli: None. **C. Elgueta:** None. **J.J. Letzkus:** None. **M. Bartos:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

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Program #/Poster #: PSTR110.14/SS5

Topic: H.08. Learning and Memory

Support: NIH R01MH112733

Title: Evaluating the impaired hippocampal circuitry in schizophrenia sheds light on the neural mechanisms underlying pattern separation

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Abstract: The ability to distinguish new from formerly seen similar items, referred to as mnemonic discrimination, is thought to rely on the hippocampus. Schizophrenia is linked to hippocampal impairments such as reduced volume, molecular and cellular abnormalities, and systems level dysfunction. Yet the functioning of hippocampal circuitry during mnemonic discrimination in individuals with schizophrenia is not clear. We examined neural activation and behavioral performance during a mnemonic discrimination task in first diagnosis medication naïve or minimally-treated patients with schizophrenia and delusions (n=45) and matched healthy controls (n=49) at baseline and after 8 weeks of antipsychotic treatment. Using a mnemonic pattern separation task, participants viewed a series of novel, repeated, and similar but not identical images and made mnemonic judgments while undergoing high-resolution fMRI imaging. Patients' performance in correctly identifying an item as old was impaired compared to healthy controls. In addition, pattern separation performance, defined by the proportion of correct responses to similar items minus the "similar" responses to new items was reduced in patients. The severity of delusions in patients was significantly correlated with these behavioral impairments. Analysis of univariate BOLD activity in hippocampal subfields during the task as well as its relationship with performance on a trial by trial basis revealed significant differences between patients and controls at baseline during the identification of similar items. Unlike controls, trial-level univariate response during similar trials in hippocampal subfields did not predict behavior in patients. After treatment, however, this relationship improved in all subfields and became significant in dentate gyrus (DG). In contrast to the impairment in hippocampal circuitry in patients during this task, the univariate response in cortical regions was similar to controls. In cortical regions, we found a significant trial-level relationship between univariate response and performance during similar trials in patients at baseline. Our results indicate a strong relationship between mnemonic judgment behavior and delusions. By modeling neural response in relation to behavior, we were able to isolate the involvement of DG in pattern separation. In addition, our findings suggest a compensatory role for cortical contributions to pattern separation in patients with first-episode schizophrenia. Together these results provide new insights into the systems level contributions to mnemonic discrimination and the impacts of schizophrenia and antipsychotic treatment.

Disclosures: **A. Zadbood:** None. **Y. Tang:** None. **W. Su:** None. **H. Hu:** None. **G. Capichioni:** None. **F. Ando:** None. **C. Gasser:** None. **O. Bein:** None. **W. Yu:** None. **J. Wang:** None. **D. Goff:** None. **L. Davachi:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.15/SS6

Topic: H.08. Learning and Memory

Support: Columbia University Precision Medicine Initiative
NIMH R21MH122965

Title: Modulation of infraslow oscillation in the dentate gyrus during Non-REM sleep

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Abstract: The importance of sleep in memory consolidation is well-established, with the hippocampal CA1 and CA3 subregions playing a crucial role in this process. The current working hypothesis postulates that episodic memory traces captured during waking hours are replayed in the hippocampal CA1-CA3 areas and transferred to the cortex for long-term storage during sleep. While the entorhinal cortex provides sensory and spatial information primarily to the hippocampus via the dentate gyrus (DG), the DG has traditionally been regarded as a "silent partner" in memory consolidation. The transfer of captured memory traces from the DG to downstream hippocampal areas remains largely unknown. To investigate this, we used optical imaging tools to record neural activity in the DG during different sleep stages. Strikingly, we found that many of the DG cells are even more active during sleep than wakefulness and the populational activity in the DG slowly oscillates during non-REM (NREM) sleep. The cycles of this oscillatory activity coincided with microarousals and were tightly locked to brief serotonin (5-HT) bursts during NREM sleep. Pharmacological blockade of 5-HT1a receptors abolished the calcium oscillations in the DG. Furthermore, the genetic knockdown of 5-HT1a receptors in the DG lead to memory impairment in spatial and contextual memory tasks. Together, our findings suggest that serotonin-driven infraslow calcium oscillations in the DG during NREM sleep are necessary for memory consolidation.

Disclosures: **G.F. Turi:** None. **X. Chen:** None. **S. Teng:** None. **Y. Peng:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.16/SS7

Topic: H.08. Learning and Memory

Title: Does reactivation of hippocampal drug-related engrams serve as a re-experiencing effect of the drug-related state including locomotor sensitization effects, or are these separate?

Authors: *M. R. WILSON[1,3], S. A. ARORA[1,2], L. F. PAPANIKOLAOU[1], L. H. EDWARDS[1], S. CAÑUELAS DEL VALLE[1], P. CHATTERJEE[1], H. K. ASGARALI[1], R. RIVERA[1,4], S. L. GRELLA[1,2];
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Abstract: A variety of studies have used neuronal tagging strategies to label the cells involved in a particular experience and to later reactivate these cells to drive different behaviors including fear and reward-related behaviors. We are interested in what aspects of the tagged experience are recapitulated when memories are artificially reactivated using optogenetics. To that end, using the doxycycline (DOX) inducible Tet-tag system to express ChR2 driven by the c-Fos promoter, we tagged a cocaine-related engram in the dorsal dentate gyrus (DG) and later reactivated this engram to assess locomotor sensitization effects. Initially, in male c57BL/6 mice we labeled a cocaine-related memory where mice were injected intraperitoneally (15mg/kg) and then placed in a novel clean cage for 1hr. When these animals were back on DOX, we reactivated this memory in an open field to assess measures of locomotion and found no effect. We then ran a similar experiment; however, we wanted the mice to demonstrate a locomotor sensitization effect with cocaine and then assess whether subsequent reactivation of a tagged cocaine experience would induce this behavior. In male, and female c57BL/6 mice that underwent cocaine conditioned place preference, we tagged the first cocaine conditioning session where we administered an intraperitoneal injection of cocaine (15mg/kg) and placed the mice in the drug-paired chamber for 15 minutes. Although we did see locomotor sensitization in these mice during conditioning, we did not see any effect on locomotion following extinction, when we reactivated this DG-mediated memory in a novel clean cage. Finally, since experiments 1 and 2 both involved tagging the animal's first exposure to the drug, we decided to run a third experiment where this was not the case. Here, male and female c57BL/6 mice again demonstrated cocaine-induced locomotor sensitization as we administered cocaine injections (15mg/kg, i.p.) every other day (D1, D3, D5, D7) subsequently placing them in context A for 45 minutes, and we either tagged the first (D1) or the fourth (D7) cocaine exposure. This was followed by a test for locomotor sensitization that lasted 15 min where we optically reactivated the DG-mediated tagged engram in either context A or context B.

Disclosures: M.R. Wilson: None. **S.A. Arora:** None. **L.F. Papanikolaou:** None. **L.H. Edwards:** None. **S. Cañuelas del Valle:** None. **P. Chatterjee:** None. **H.K. Asgarali:** None. **R. Rivera:** None. **S.L. Grella:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.17/SS8

Topic: H.08. Learning and Memory

Title: Locus coeruleus modulation of hippocampal fear memory traces: hippocampal flexibility and context generalization

Authors: *H. K. ASGARALI[1], L. F. PAPANIKOLAOU[1], M. M. MCANESPIE[1], S. A. ARORA[1,2], L. H. EDWARDS[1], P. CHATTERJEE[1], S. CAÑUELAS DEL VALLE[1], R. RIVERA[1,3], A. STRATMANN[1], G. PATEL[1], S. L. GRELLA[1,2];
[1]Neurosci., [2]Psychology, Loyola Univ. Chicago, Chicago, IL; [3]Computer Engin., Univ. of Illinois Chicago, Chicago, IL

Abstract: Post-traumatic stress disorder (PTSD) is a mental health condition (with a lifetime prevalence of 7.8% in the US) that is triggered by experiencing a traumatic event. It is unknown why certain subsets of individuals are more vulnerable to developing PTSD than others, with women affected twice as much as men. This disorder is often characterized by flashbacks, nightmares, rumination, and intrusive thoughts related to the event. A hallmark symptom of PTSD is fear generalization where acquired fear responses are expressed in non-threatening environments. Memory updating is an adaptive mechanism, which allows an organism to access the most relevant information from memory. We hypothesize that fear generalization may stem from memory updating impairments involving a failure to remap trauma-related memory traces in the presence of novel information (e.g., safety signals), and the persistent recall of these traces in the presence of non-trauma related contexts or stimuli. To examine the effects of stress on the stability and flexibility of contextual representations in the dorsal dentate gyrus (DG), we used a viral-based neuronal tagging strategy (AAV9-c-Fos-tTA-TRE-eYFP) to label cells involved in encoding a strong fear conditioning experience in male and female Th-Cre mice. Reconsolidation, where previously consolidated memories are recalled, can serve as a mechanism to update memories, specifically in the presence of new information. Previous evidence shows that the norepinephrine (NE) system is dysregulated in PTSD, and we have shown that the pathway from the locus coeruleus (LC) (site of NE synthesis) to the hippocampus is involved in remapping hippocampal contextual representations and may constitute an important pathway in memory updating. To assess whether optical activation of LC terminals in the DG (20Hz) during reconsolidation (in either the fear context or a safe context) would promote remapping of DG engrams and reduce generalization, we also infused these mice with AAV5-Ef1a-DIO-(ChR2)-mCherry in the LC and implanted an optical fiber over the DG. We hypothesized that this optical neuromodulatory manipulation would enhance discrimination and facilitate extinction restoring cognitive flexibility. Mice were tested for recall in either the fear context or the safe context. Our future goal is to also identify genetic factors that may contribute to these impairments and the way in which they interact with experience to confer susceptibility or resilience to stress.

Disclosures: **H.K. Asgarali:** None. **L.F. Papanikolaou:** None. **M.M. McAnespie:** None. **S.A. Arora:** None. **L.H. Edwards:** None. **P. Chatterjee:** None. **S. Cañuelas del Valle:** None. **R. Rivera:** None. **A. Stratmann:** None. **G. Patel:** None. **S.L. Grella:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.18/SS9

Topic: H.08. Learning and Memory

Title: The role of cocaine and extinction-associated engrams in driving / preventing drug-seeking behavior using conditioned place preference

Authors: *L. H. EDWARDS[1], S. A. ARORA[1,2], M. R. WILSON[1,3], L. F. PAPANIKOLAOU[1], H. K. ASGARALI[1], P. CHATTERJEE[1], L. F. REYNOLDS[4], S. COELLO[4], G. PATEL[1], R. RIVERA[1,5], A. STRATMANN[1], M. M. MCANESPIE[1], S. CAÑUELAS DEL VALLE[1], S. L. GRELLA[1,2];
[1]Neurosci., [2]Psychology, Loyola Univ. Chicago, Chicago, IL; [3]Lab. of Behavioral and Genomic Neurosci., Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD; [4]Psychological and Brain Sci., Boston Univ., Boston, MA; [5]Computer Engin., Univ. of Illinois Chicago, Chicago, IL

Abstract: Addiction is characterized by a continual propensity to relapse. Relapse-prevention strategies aimed at reducing the likelihood and severity of relapse following abstinence, focus on reducing cravings that lead to drug-seeking. Factors precipitating drug-seeking include exposure to drug-related cues, to the drug itself, and to stress. One factor not yet directly investigated is the contribution of drug-related memories. Conditioned place preference (CPP) has been used to study the rewarding aspect of drugs and the reinstatement model has been used to study relapse. To investigate the role of memories in promoting relapse, we tagged dorsal dentate gyrus (DG) cells involved in encoding a cocaine-related memory (the first conditioning session) using the doxycycline-inducible, Tet-tag system to express ChR2 driven by the c-Fos promoter, in male and female c57BL/6 mice. Mice underwent cocaine (15 mg/kg, i.p.) CPP training where they learned to associate cocaine with one side of the chamber and saline with the other. Following conditioning, preference for the cocaine side was extinguished and then reinstated using either a priming injection of cocaine (7.5mg/kg) (or saline) compared to optical reactivation of the tagged cocaine-related memory (20Hz, ChR2 or eYFP), thus exploring whether reinstatement can be primed via the memory of a drug in comparison to the drug itself and whether these effects may be additive (or protective). In the second experiment, we again tagged the first CPP conditioning session and then either administered cocaine (15 mg/kg) or optically reactivated the tagged memory (20 Hz) (these mice received saline) for each cocaine conditioning session thereafter to assess whether reactivation of the first drug-related experience was sufficient to drive a conditioned place preference. Finally, in the third experiment, following cocaine CPP, we ran extinction training and tagged the last extinction session. We then reactivated the cells that were

involved in encoding this extinction session during a drug-primed (7.5mg/kg, i.p.) reinstatement test to assess whether this would interfere with or inhibit cocaine-induced reinstatement.

Disclosures: L.H. Edwards: None. **S.A. Arora:** None. **M.R. Wilson:** None. **L.F. Papanikolaou:** None. **H.K. Asgarali:** None. **P. Chatterjee:** None. **L.F. Reynolds:** None. **S. Coello:** None. **G. Patel:** None. **R. Rivera:** None. **A. Stratmann:** None. **M.M. McAnespie:** None. **S. Cañuelas del Valle:** None. **S.L. Grella:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.19/SS10

Topic: B.08. Epilepsy

Support: KAKENHI 21K06434

Title: Simulation analysis of stimulus-induced hyperexcitability of hippocampal mossy fiber

Authors: *H. KAMIYA;
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Abstract: Modification of axonal excitability occasionally causes the firing of action potentials either from the physiological initiation site mostly at the axon initial segment, or from the ectopic sites for the spike generation. It has been demonstrated that the repetitive high-frequency stimulation of hippocampal mossy fibers resulted in burst firing possibly originating ectopically from distal axons, although the underlying mechanisms remain elusive. In this study, we explore the mechanisms by computational approaches using a simple model of hippocampal mossy fibers implemented with experimentally obtained properties of ionic conductances. When slight depolarization of distal axons was given in conjunction with the high-frequency stimulus, repetitive spontaneous discharges were triggered after cessation of the stimulus to the mossy fibers and lasted for a prolonged period after the stimulus. It should be noted that the spontaneous discharges recorded from distal axons precede those recorded from the soma, suggesting that the spontaneous discharge were generated from distal axons and propagated antidromically to the soma. When the model of the voltage-dependent potassium channel was exchanged with a model of a non-inactivating type potassium channel, the spontaneous burst was not induced by the repetitive stimuli. These results suggested that accumulated inactivation of potassium channels during repetitive action potentials may modify the excitability of mossy fibers and cause ectopic spiking from different sites of spike initiation.

Disclosures: H. Kamiya: None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.20/SS11

Topic: A.02. Postnatal Neurogenesis

Support: AS intramural grant

Title: Mechanisms regulating the integration of adult-born mossy fiber boutons into mature neural circuits

Authors: H.-C. CHANG[1], C.-C. HUANG[2], ***H.-J. CHENG**[1];
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Abstract: Adult hippocampal neurogenesis (AHN) is critical for learning and memory. Disruption of this process is implicated in neuropsychiatric diseases that undermine cognition in the brain. Using a reporter mouse line, we investigated the development and synaptic integration of newborn mossy fiber boutons in the adult hippocampus. We found that the potential for adult-born mossy fibers to form *de novo* bouton synapses with existing mature CA3 pyramidal cells in aged brain is significantly reduced, and the pre-existing mature mossy fiber boutons are replaced when the adult-born mossy fiber boutons are formed in aged brain. These results indicate changes of bouton synapse formation from young adult to aged hippocampus. We are currently using a novel spatial proteomics technique to identify candidate molecules that might regulate the formation of adult-born mossy fiber boutons in young adult and aged hippocampus to address why the adult-born mossy fibers in the aged brain lose their ability to form *de novo* synapses during synaptic integration. The answers to these questions might help us understand the specific functional role of AHN in the aged brain.

Disclosures: H. Chang: None. **C. Huang:** None. **H. Cheng:** None.

Poster

PSTR110. Dentate Gyrus

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR110.21/SS12

Topic: H.08. Learning and Memory

Support: SFB 936

Title: Activity-dependent FOS expression in the hippocampus depends on the epigenetic state of individual neurons

Authors: ***A. FRANZELIN**[1,2], P. J. LAMOTHE-MOLINA[2], M. ANISIMOVA[2], C. E. GEE[2], T. G. OERTNER[2];

[1]Univ. Med. Center, Hamburg, Hamburg, Germany; [2]Inst. for Synaptic Physiol., Hamburg, Germany

Abstract: The immediate early gene FOS has been used to identify ensembles of neurons active during memory formation and recall. But do all neurons active in a task express FOS? Is FOS expression regulated similarly in different types of hippocampal neurons? FOS promoter-dependent expression of the photoconvertible calcium indicator CaMPARI was driven in mouse dentate granule (DG) neurons during training in the Morris Water Maze (WM). During probe trials on subsequent days, CaMPARI photoconversion indicated that many of these neurons had calcium transients and thus were active. Their importance for memory recall was demonstrated as mice were worse at recalling platform position when the neurons were selectively inhibited during subsequent day probe trials. Curiously however, these FOS-tagged DG neurons rarely expressed FOS despite the clear indications they were both active and important for recalling the memory. Instead, we observed strong expression of ΔFOSB in DG neurons after probe trials on subsequent days. ΔFOSB is a highly stable splice variant of FOSB, which accumulates in the hippocampus after epileptic events and interferes with FOS expression via epigenetic mechanisms. In contrast to the DG, FOS was present and ΔFOSB absent in many CA1 pyramidal neurons after WM training. We further investigated the cell-type differences in FOS and ΔFOSB expression in organotypic hippocampal slice cultures. Interestingly, CA1 neurons in slice cultures do express ΔFOSB when stimulated with bicuculline. Furthermore, FOS expression is significantly lower in both DG and CA1 after bicuculline treatment on subsequent days. Bicuculline-induced FOS expression is restored by inhibiting HDACs on subsequent days. At the population level, stimulation-induced FOS expression positively correlates with increased intracellular calcium in DG, CA1 and CA3 neurons. At the level of individual neurons however, we could find no correlation, suggesting that a slice-wide increase in activity drives FOS rather than activity of the individual neuron per se. We also consistently observe that $PCP4^+$ neurons in the hilus, CA2 and subiculum express significantly less FOS than other hippocampal neurons. Our findings show that the amount of FOS expressed by hippocampal neurons in a repeated behavioral paradigm or in response to repeated stimulation is not consistent. Rather, the magnitude of the FOS response is strongly influenced by the history of activity and cell type. We suggest that the physiological role of ΔFOSB is to drive pattern separation in the dentate gyrus by modulating the epigenetic state of individual neurons.

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Poster

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Program #/Poster #: PSTR110.22/SS13

Topic: H.08. Learning and Memory

Support: NIA Grant R01 AG057705-01
NIA Grant R01 AG076937-01

Title: Age- and irradiation-dependent decline in cognitive flexibility is associated with compromised hippocampal neurogenesis

Authors: *E. M. AMELCHENKO[1], D. V. BEZRIADNOV[2], O. A. CHEKHOV[1], A. A. IVANOVA[3], A. A. KEDROV[2], K. V. ANOKHIN[4], A. A. LAZUTKIN[1], G. ENIKOLOPOV[1]; [1]Anesthesiol. and Ctr. for Developmental Genet., Stony Brook Univ., Stony Brook, NY; [2]P.K. Anokhin Res. Inst. of Normal Physiol., Moscow, Russian Federation; [3]Inst. of Higher Nervous Activity and Neurophysiol. RAS, Moscow, Russian Federation; [4]Inst. for Advanced Brain Studies, Lomonosov Moscow State Univ., Moscow, Russian Federation

Abstract: Cognitive function in animals is critically dependent on age and or on occasional exposure to adverse environmental conditions, such as ionizing radiation. While the impact of these factors on neurogenesis is well documented, the full range of their effect on behavior remains unclear. Here, we investigated the effect of normal aging and gamma-radiation on learning, memory, and cognitive flexibility. Towards this aim, we developed a novel hippocampus-dependent behavioral assay, the context discrimination Morris water maze (cdMWM) task, which requires integrating various contextual cues and continuously adjusting the search strategies. In one experimental series we compared the performance of mature adult and late middle-aged mice (6 and 14 months old, respectively), i.e., prior to the overt manifestation of age-related impairments. In another series we exposed adult animals to 5 Gy of gamma-radiation. All animals were consecutively trained in spatial MWM (sMWM), reversal MWM (rMWM), and cdMWM tasks. Both aged and irradiated mice performed successfully in the sMWM. However, in rMWM the aged mice were less efficient than the respective control group, employing fewer spatially precise strategies and showing longer escape latencies. Finally, both aged and irradiated mice demonstrated significant deficits in cdMWM, as evidenced by each of the several applied metrics of learning and memory. Notably, additional training restored the performance of the affected groups to the level of the control groups. In addition to behavioral changes, we observed a significant decrease in neurogenesis levels in the aged and irradiated groups. Notably, specific components of the cdMWM training after irradiation required differential recruitment of preexisting and adult-born neurons, with the latter becoming competent at 12 weeks, a significantly later age than revealed by other types of assays. Remarkably, we found a profound correlation between the numbers of mature and immature adult-born hippocampal neurons in individual mice and their performance in the cdMWM. Together, our findings suggest that aging and exposure to gamma radiation do not impede the acquisition of new experiences; however, both groups exhibit transient deficits when modifications to the relevant experience and readjustment of the previously employed strategies, i.e., the core elements of cognitive flexibility, are required. Finally, the remarkable correlation in individual animals between neurogenesis levels and performance in a complex task indicates a potential link between adult hippocampal neurogenesis and cognitive flexibility.

Disclosures: E.M. Amelchenko: None. **D.V. Bezriadnov:** None. **O.A. Chekhov:** None. **A.A. Ivanova:** None. **A.A. Kedrov:** None. **K.V. Anokhin:** None. **A.A. Lazutkin:** None. **G. Enikolopov:** None.

Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

Location: WCC Halls A-C

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Title: Multiplexed interhemispheric information exchange in the retrosplenial cortex

Authors: *O. AHMED[1], M. GHOSH[2], A. B. JOHNSON[2], A. LORENZO GONZALEZ[3], A. LEKANDER[2], V. HETRICK[2];
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Abstract: Rhythmic gamma-band communication within and across cortical hemispheres is critical for optimal perception, navigation, and memory. We have recently shown that even faster 140 Hz rhythms are robustly anti-phase across cortical hemispheres, visually resembling splines, the interlocking teeth on mechanical gears. Splines are strongest in superficial granular retrosplenial cortex, a region important for spatial navigation and memory. While splines and associated neuronal spiking are anti-phase across retrosplenial hemispheres during navigation and REM sleep, gamma-rhythmic interhemispheric communication is precisely in-phase. Gamma and splines occur at distinct points of a theta cycle and thus highlight the ability of interhemispheric cortical communication to rapidly multiplex in-phase (gamma) and antiphase (spline) modes within individual theta cycles. Here, we show that this coding scheme shifts systematically across navigational behaviors and REM sleep epochs. Our results highlight state-dependent changes in multiplexed communication protocols in the retrosplenial cortex.

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Poster

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Title: Cell-type-specific cholinergic control of retrosplenial cortex with implications for angular velocity coding across brain states

Authors: *C. I. RYBICKI-KLER[1,2], I. JEDRASIAK-CAPE[2], I. BROOKS[2], M. GHOSH[2], E. K. BRENNAN[2], S. KAILASA[3], T. EKINS[2], O. J. AHMED[2,4,5,6,7];
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Abstract: Cortical acetylcholine levels increase during spatial navigation. Cholinergic muscarinic activation induces persistent firing of cortical principal neurons, providing a key cellular basis for theories of spatial working memory and path integration. The granular retrosplenial cortex (RSG) is important for successful spatial navigation and contains multiple subtypes of principal cells, including low-rheobase (LR) and regular spiking (RS). We have previously demonstrated that these two cell types participate in distinct, parallel circuits to process navigationally relevant inputs to the RSG. Here, we show that the transcriptomically, morphologically and biophysically distinct LR cell-type has a very different expression profile of cholinergic muscarinic receptors when compared to its RS neighbors. To investigate the cell type-specific response to activation of muscarinic receptors, we performed whole-cell recordings of RS (n=57) and LR (n=22) cells and characterized their response to muscarinic agonists. Consistent with our transcriptomic results, LR neurons did not show any cholinergically-evoked persistent firing, in stark contrast to all other principal neuronal subtypes examined within the RSG and across the frontoparietal cortex. These results were similar for both male and female mice. Using an integrate-and-fire model of the LR neuron, we show that this lack of persistence allows LR cells to rapidly compute angular head velocity, independent of cholinergic changes across brain states. Thus, the LR neuron is a unique cell type, optimized for rapid state-independent computations needed to encode angular head velocity, a critical component of spatial navigation.

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Poster

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Support: NIH R34NS127101
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Title: The retrosplenial transcriptome in mice, rats, and preclinical Alzheimer's disease

Authors: *I. A. W. BROOKS[1], I. JEDRASIAK-CAPE[1], C. RYBICKI-KLER[3], T. EKINS[2], O. J. AHMED[1];
[1]Psychology, [2]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]Univ. of Michigan Neurosci. Grad. Program, Ann Arbor, MI

Abstract: The granular retrosplenial cortex (RSG) serves as an important integrator of spatial and sensory information, but the cell-type-specific contributions to its unique computational abilities remain unclear. We have previously identified a transcriptomically, morphologically, physiologically, and computationally distinct cell type in the RSG of mice: the low rheobase (LR) cell. Here, we first generated 10x Genomics single-cell RNA-seq datasets using samples collected from both wildtype mice and rats. We confirmed the framework of major cortical cell types remained largely preserved between mice and rats, including the dominant presence of the LR cell-type in both species. However, we also identified numerous interspecies differences between mice and rats. Next, we compared the null mouse RSG transcriptome to that of a preclinical mouse model of Alzheimer's disease (5xFAD). These comparisons yielded thousands of differentially expressed genes across conditions and cell types. The 5xFAD comparison replicated some observations of transcriptomic Alzheimer's studies in humans, while identifying several dysregulated genes with implications for altered neurotransmission and circuit dynamics. Together this work establishes a transcriptomic database for the study of the retrosplenial cortex across species and across disease states.

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Poster

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Topic: H.09. Spatial Navigation

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Title: Diverse representations of visual information in the medial entorhinal cortex

Authors: *O. DUBANET, M. J. HIGLEY;
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Abstract: Although spatial navigation and memory rely centrally on the hippocampus and entorhinal cortex, visual information is critical to provide information about the environment and support error correction during path integration. However, the neural pathways by which visual information is routed to these structures are largely unknown. The medial entorhinal cortex (MEC) receives monosynaptic inputs from several visual areas in the neocortex, suggesting that

it may directly encode low-level sensory features that contribute to hippocampal function. We addressed this question using multi-electrode recordings of MEC cell populations in head-fixed, freely running mice presented with visual stimuli comprising patches of contrast-modulated drifting gratings with varied orientation, spatial frequency, and size. Surprisingly, more than 50% of MEC cells exhibited robust, short-latency responses to visual input. Individual cells exhibited three broad categories of response profiles: a sustained increase in firing rate throughout the stimulus presentation, transient increased firing at stimulus onset, or suppression of activity during the stimulus. Spike correlations between pairs of simultaneously recorded cells suggest these categories may correspond to distinct populations with differential interconnectivity. Additionally, activity-dependent labeling of cells with CaMPARI2 combined with immunolabeling revealed that visually-responsive neurons are predominantly located in layer 5 and express Ctip2 marker. Visual responses were monotonically dependent on increasing stimulus contrast and size were not selective for orientation or spatial frequency. Moreover, spontaneous and evoked activity were highly modulated by fluctuations in behavioral state and coupled to ongoing network dynamics (e.g., theta and gamma-band oscillations). Retrograde tracing showed robust projections to the MEC originating from higher order visual areas including the retrosplenial cortex (RSC), with modest projections arising from V1. Optogenetic silencing of RSC terminals within the MEC using eOPN3 substantially reduced visual responses magnitude of MEC cells. Overall, our results suggest that deep layer MEC neurons can diversely encode low-level visual information via inputs from the RSC, providing a mechanism by which sensory representations can be routed to the hippocampus and contribute to spatial navigation and memory.

Disclosures: O. Dubanet: None. **M.J. Higley:** None.

Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

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Topic: H.09. Spatial Navigation

Support: University of Toledo Research Funds

Title: Sex differences in brain activation for MRT using fMRI in adults

Authors: *J. RAZZAQUE[1], A. S. COTTON[2], K. LE[1], H. A. CHAUDHRY[1], X. WANG[1], T. SUBRAMANIAN[1];
[1]Neurol., Univ. of Toledo, Toledo, OH; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Mental Rotation Tasks (MRT), testing spatial visualization, have been consistently reported in research to exhibit one of the largest and most significant sex differences in terms of performance and brain activation, with men generally outperforming women in this cognitive domain. While fMRI research has discovered an array of cortical activation patterns for MRT,

extending beyond the widely acknowledged involvement of the parietal region, the differential activation of various brain areas warrants further scrutiny.Four male and six female, right-handed healthy volunteers with the mean age of 54.1 ± 6.1 (SD) underwent fMRI imaging while performing a 2-part MRT paradigm. In **MRT A,** baseline conditions were achieved by Fourier transformations of the original stimuli and rest periods between rotational trials of MRT. In **MRT B,** rotational stimuli were interspersed with several control conditions: rest, identical cube figures and bidirectional arrows. For MRT A, analysis of response accuracy revealed differences approaching significance; males scoring 31% vs females 9%, but reaction times revealed no significant difference. For MRT B, percent response accuracy was 62.5 ± 23.1 vs 65.3 ± 17.1 and reaction times(s) were 3.78 ± 0.44 (SD) vs 4.08 ± 0.28 (SD), for males vs females respectively. For our exploratory analysis, statistical images were generated using FSL 5.0.10 using a Z-threshold of2.3 and cluster p-threshold of 0.05. A single-sample one-sided Z-test, for all subjects identified significant overlapping clusters of activations in bilateral mid-occipital, superior and inferior parietal, superior frontal, cerebellar and right inferior frontal operculum and precuneus for the contrast comparing MRT to pattern matching in MRT A. For MRT B, overlapping clusters of activations in bilateral lingual gyrus, bilateral superior and right inferior frontal, bilateral superior and inferior parietal, mid-occipital regions to name a few, were found for the contrast comparing MRT to direction labeling. A two-sample T-test revealed no significant differences in brain activation between female and male subjects for MRT A, which could be due to our smaller preliminary sample size. However, for MRT B, men demonstrated significantly greater activation in the dorsal anterior cingulate (dACC) compared to women (Z-peak = 3.39; peak MNI coor. = -12, 30, 16 mm; voxel # = 502) for the contrast comparing MRT to direction labeling.
Results from our ongoing longitudinal study will add to our elucidation of areas of cerebral activations during MRT as we continue to accrue subjects from both sexes.

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Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

Location: WCC Halls A-C

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Topic: H.09. Spatial Navigation

Support: Otto Hahn Group founded by Max Plank Society

Title: Connectomic analysis of the parasubiculum-enthorinal circuit

Authors: *E. GRASSO[1], M. SIEVERS[2], H. SCHMIDT[1];
[1]Ernst Strüngmann Inst., Frankfurt am Main, Germany; [2]Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: The spatial representation system is fundamental to understand how we perceive the surrounding environment. The *grid cells* located in the *Medial Entorhinal cortex* (*MEC*), the *head-direction cells* as well as the *border cells* located in the *Parasubiculum* (*PaS*), are thought to crucially contribute to navigation. Physiological recordings have demonstrated that the principal neurons in all layers of the MEC receive inputs from the PaS. However, the neuronal circuits underlying this complex organization are still unknown. Here, we used a high-resolution 3D-EM dataset encompassing parts of the mouse PaS and MEC (sized 1.5 mm × 1.1 mm × 358.4 µm at 4 × 4 × 35 nm³ resolution) to investigate the synaptic contacts between the axons of PaS neurons and their postsynaptic targets in MEC. Both pyramidal and stellate cells were contacted by the PaS axons, with a focus on L2. Targets included L2, L3 and deep layer pyramidal neurons. We also found precise geometric configurations of PaS axons. We are currently obtaining a more comprehensive connectomic mapping of the involved circuits, aimed at understanding the architecture of possible head direction inputs to MEC neurons.

Disclosures: **E. Grasso:** None. **M. Sievers:** None. **H. Schmidt:** None.

Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

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Topic: H.09. Spatial Navigation

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Title: Histological analysis of Perirhinal (PER) and Lateral Entorhinal Cortex (LEC) of male mice using ImageJ

Authors: *B. B. AOYAMA, A. S. VIEIRA;
IB - DBEF (Biology Institute- Dept. of Functional and Structural Biology), State Univ. of Campinas, Campinas, Brazil

Abstract: The perirhinal cortex (PER) plays an important role in object recognition memory and comprises two horizontal bands, areas 35 and 36, that have different cytoarchitectures and connections. The lateral entorhinal cortex (LEC) processes visual and spatial information, receives direct inputs from PER, and projects it to the hippocampus and other cortical structures. The LEC is subdivided into dorsolateral (DLE) and ventral intermediate (VIE) bands, which have different cytoarchitectures and connections. This study aims to investigate the morphological characteristics of 35 and 36 areas of PER, DLE, and VIE from LEC. Male C57BL/6 mice (n=3) were submitted to transcardially perfusion with 4% formaldehyde. The brains were coronally sectioned, and serial slices (40 µm) were incubated in a PBS solution

containing 0.9% saline. For each brain, sections were selected at the rostral level (bregma - 1.77), intermediate level (bregma - 2.38), and caudal level (bregma - 4.04). Microscopy (Leica®) was used to capture images, and histology was analyzed using ImageJ. We observed increased compaction of the II/III layers and a general non-linear organization of the cellular layers in areas 35 and 36 compared to the DLE and VIE bands of the LEC at intermediate and caudal levels. The latter bands exhibit a columnar cellular organization with an apparent cell-free zone separating the cellular layers. Although both the DLE and VIE bands demonstrated columnar cellular organization, a prominent cell-free zone separating layers II and III was observed in the VIE band compared to the same layers in the DLE. Regarding the morphological differences between the 35 and 36 areas of PER, the cellular layers appeared disorganized and narrow in area 35 compared to the same layers in area 36 along the rostrocaudal axis. Therefore, our results demonstrated the importance of morphology and anatomical location in accurately identifying these regions. These findings might contribute to future studies by providing molecular data for specific subpopulations within these regions.

Disclosures: B.B. Aoyama: None. **A.S. Vieira:** None.

Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

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Topic: H.09. Spatial Navigation

Support: Marga und Walter Boll-Stiftung grant 210-05. 01-21

Title: Cortical correlates of decision making strategies in human wayfinding

Authors: *J.-Y. HUANG[1], O. A. ONUR[2], D. MEMMERT[1], O. BOCK[1];
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Abstract: Wayfinding requires us to decide which direction to take at intersections to reach a desired location. Studies have identified five distinct cognitive strategies for such decision making, three relying on an egocentric reference frame and two on an allocentric reference frame (Rinne et al, 2022). Previous research has observed that egocentric (response-based) strategies primarily engage posterior parietal regions and striatum (i.e., caudate), while allocentric (place-based) strategies predominantly involve the medial temporal lobes (e.g., hippocampal, parahippocampal). Specifically, the caudate is associated with decision making of memory from prior responses, whereas the hippocampus is relevant to the formation and maintenance of cognitive maps of the environment. However, the differential neural correlates of those five decision making strategies are still unclear. We therefore investigated those cortical correlates in young adults who were asked to find their way through five types of strategy-specific virtual mazes. The first trip through each maze was externally guided, and the subsequent five trips

were self-guided. We measured cortical activity using a 64-channel EEG system connected to an ActiChamp Plus amplifier. Independent component analysis identified clusters of cortical activity related to wayfinding in the frontal, parietal, temporal, occipital, and limbic lobes. Importantly, the pattern of specific absolute spectral power in those clusters varied between strategy-specific mazes. From this, we conclude that different decision making strategies were associated with a varying processing demand across brain regions.

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Poster

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Cajal Blue Brain (PTI-BLUEBRAIN)
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Title: Common and differential morphological features of human occipital and temporal pyramidal cells

Authors: *R. BENAVIDES-PICCIONE[1,2,3], L. BLAZQUEZ-LLORCA[4], A. KASTANAUSKAITE[1], I. FERNAUD-ESPINOSA[2], S. TAPIA-GONZÁLEZ[5], J. DEFELIPE[1,2,3]; [1]Cajal Inst., Madrid, Spain; [2]Lab. Cajal de Circuitos Corticales, Univ. Politécnica de Madrid, Madrid, Spain; [3]Ctr. de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), ISCIII, Madrid, Spain; [4]Dept. de Anatomía y Anatomía Patológica Comparada. Facultad de Veterinaria. Univ. Complutense de Madrid, Madrid, Spain; [5]Facultad de Medicina. Univ. Castilla La mancha, Albacete, Spain

Abstract: The basic building block of the cerebral cortex, the pyramidal cell, has been shown to be characterized by markedly different dendritic structure among layers, cortical areas and species. Functionally, differences in the structure of their dendrites and axons are critical in determining how neurons integrate information. However, within the human cortex, the pyramidal dendritic and axonal morphology has not been quantified in detail. In the present work, we performed intracellular injections of Lucifer Yellow and 3D reconstructed from confocal microscopy images over 200 pyramidal cells, including apical and basal dendritic and local axonal arbors, from human occipital (Brodmann's area 17) and temporal (Brodmann's areas 20 and 21) cortex. We found that human pyramidal neurons from BA20 and BA21 were larger and displayed different apical and basal structural organization compared to those in BA17. Furthermore, these neocortical cells exhibited certain common and differential

morphological features compared to previously published human hippocampal (CA1 field) pyramidal neurons. The present study further emphasizes the areal and species variations in pyramidal cell structure.

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Poster

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Topic: H.09. Spatial Navigation

Support: Max Planck Society
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Title: Differential theta rhythm generation in the medial septum and the supramammillary nucleus

Authors: *M. MOZAFFARILEGHA, H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Cortical synchrony has been considered to play a key role in integrating distributed information across the brain. While previous studies reported that theta oscillations are dynamically coordinated between the prefrontal cortex and the hippocampus depending on behavioral demands, how such interregional synchrony is desirably controlled in the brain remains unclear. The primary sources of theta oscillations have been described in two subcortical regions, the supramammillary nucleus (SUM) and the medial septum (MS). We hypothesize that the modulations of these two oscillators may underlie dynamic interregional coupling. To test this idea, we performed simultaneous recordings from the SUM, MS, medial prefrontal cortex (mPFC), and area CA1 of the hippocampus. We first compared theta oscillations in SUM and MS when the animal performed two different behavioral tasks, either a random foraging task or a goal-alternation task in a modified T-maze. We discovered a significantly lower theta coherence between SUM and MS during random foraging in both phase and amplitude components. This low coherence is not simply due to the difference in the power of theta oscillations or the animal's speed between the two tasks. Instead, we found significant differences in peak frequencies of theta-rhythmic spiking between SUM and MS neurons, implying independent generation of theta oscillations in these two regions. We also found that theta coherence between SUM and MS differs before and after the times of trajectory decisions in the T-maze alternation task. The difference in the SUM-MS theta coherence can also influence their spike-time relationships to the CA1 theta. The spike-phase locking of a subset of SUM and MS neurons relative to the CA1 theta changed during trajectory decisions, and the proportion of neurons

showing such modulation is significantly higher in SUM. The tensor component analysis on distributions of the spike field coherence across neurons in SUM and MS further confirmed that these spike-time modulations occur in the theta range and can distinguish the task phase requiring trajectory decisions. Finally, we extended this analysis to the mPFC, asking if the MS and SUM regions make differential impacts on mPFC neurons. We analyzed spike-phase locking of MS and SUM neurons to the mPFC theta and found that SUM spikes exhibit overall stronger modulations to the mPFC theta, compared to those from MS. Altogether, our findings suggest that theta rhythms in SUM and MS are independently modulated and allow for differential theta-rhythm coordination in their projection areas, which may support dynamic behavior-dependent functional coupling between cortical regions.

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Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

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Title: Memory traces of spatial goals in the ventral striatum

Authors: *N. TAKAKUWA, H. T. ITO;
Max Planck Inst. For Brain Res., Frankfurt Am Main, Germany

Abstract: When an animal initiates a goal-directed journey, it must select a particular destination in a given environment. This selection process is based, at least in part, on the memory of previous destinations and their outcomes, which likely supports an animal's flexible goal choices beyond a simple repetition of the preceding journey. Many lines of evidence suggest that the dopamine-striatum system plays a key role in predicting the value of a sensory cue or action, and we hypothesized that this system may allow the animal to evaluate different goal choices by retaining these memories. Previous studies reported that, during navigation, the dopamine release in the ventral striatum increases toward the next goal (Howe et al., 2013; Kim et al., 2020). However, whether this dopamine signal can flexibly be adapted to new goals, and if so, how a history of spatial goals can be maintained in the dopamine-striatum system, has not yet been determined. To address these questions, we recorded the activity of dopamine neurons in the ventral tegmental area (VTA). We confirmed that a subset of these neurons increased their firing toward an animal's destination, and furthermore, this goal-directed firing adapted to a new destination following the goal changes. Corresponding to this activity, we also found that the

dopamine concentration in the nucleus accumbens (NAc) measured by the dopamine sensor dLight showed the same increase and adaptation to the destination of the ongoing journey. We further explored the activity of NAc neurons and found that a subpopulation of them showed a goal-directed increase of firing rates in a similar manner as VTA neurons. However, we discovered a notable difference in NAc neurons from those in the VTA, once the animal was required to update the goals. The activity of NAc neurons increased not only toward the newly updated goals, but also the previous goals that were passed through by the animal because a reward was no longer provided there. The activity of NAc neurons thus reflects the memory of spatial goals independent of the animal's goal choice. Finally, we asked whether this previous goal memory can still influence the animal's goal decisions. To test this idea, once the animal learned a particular goal location, we abruptly stopped providing a reward there and examined the animal's subsequent behaviors. We found a significantly higher tendency for these animals to visit previous goal locations, suggesting that the goal memory is likely to provide the animal with alternative goal choices. Our results suggest that the NAc is part of the brain structure maintaining a history of spatial goals, supporting the animal's memory-guided goal decisions for navigation.

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Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

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Title: Route-invariant goal coding in the orbitofrontal cortex

Authors: *C. SHEN, H. T. ITO;
Max-Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Goal-directed navigation in a complex environment requires not only a precise estimate of the target location, but also a plan for navigational routes corresponding to a given spatial layout of the environment. While a recent study showed that neurons in the prefrontal cortex encode navigational goals (Basu et al., 2021), previous studies reported that prefrontal neurons represent an animal's movement directions or routes (Ito et al., 2015), leading to a question of whether these neurons encode a goal and a route independently or conjunctively. To address this question, we designed a new maze in which an animal is required to take different routes to reach a given goal location, allowing us to isolate representations of goal and route. We recorded the activity of OFC neurons while a rat performed this task and discovered that these neurons keep pointing to the animal's subsequent goal destination throughout the journey,

regardless of its route choices. Notably, we found that the activity of the same OFC neural population can also predict the animal's subsequent movement direction at the T-junction of the maze. Detailed analysis of ensemble neural dynamics using a dimensionality reduction method revealed that the representation of movement directions is embedded in a subspace that is nearly orthogonal to the goal-encoding subspace. This orthogonal representation may allow downstream circuits to retrieve the information of goal and route independently, likely supporting an animal's flexible navigation. Finally, we asked if the OFC's goal coding can be used even for a journey where the animal takes a new route to a given destination. To this end, we trained a goal decoder based on journeys taking specified routes, and applied the same goal decoder to a journey where the animal took a different route from those used for the decoder's training. We confirmed successful goal decoding even under this setting, implying that the OFC can form an abstract goal representation that is largely independent of exact routes or actions needed to reach there.

Disclosures: C. Shen: None. **H.T. Ito:** None.

Poster

PSTR111. Cortical Circuits: Extended Hippocampal System and Retrosplenial Cortex

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR111.13/TT1

Topic: H.09. Spatial Navigation

Support: Max Planck Society
European Research Council ('NavigationCircuits' GA714642)

Title: Neural mechanism underlying flexible goal coding by trajectory sequences in hippocampal place cells

Authors: *Z. GOLIPOUR, A. M. LOPEZ, H. T. ITO;
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Abstract: In the natural world where an animal is required to navigate to different goals to find food or shelter, the brain must keep updating a plan for the next navigation. In support of this notion, the brain's internal map system in the hippocampus not only represents the animal's own position but also exhibits the activity corresponding to the animal's subsequent trajectory when the animal is in an immobile state before starting navigation (Pfeiffer and Foster, 2013). However, whether these goal-directed sequences can flexibly be updated to new goals, and if so, how this future coding is supported by neural circuits, is still largely unclear.To address these questions, we used a linear maze with multiple water-delivery wells on the floor and trained rats to navigate between three given wells in sequence; two wells are located at both track ends and the other well is in the middle of the track. The middle goal location changes multiple times during a recording session. We recorded the activity of neurons in the dorsal hippocampal CA1 and estimated a position represented by these cells. Before the animal started navigation, the

activity of CA1 neurons represented positions beyond the animal's location, forming trajectories in the maze. We found that these represented trajectories had biases towards the animal's real paths in either the past or future. Furthermore, many of these future-directed trajectory sequences terminated at the animal's next target location and changed flexibly following the update of goal locations. We thus further explored how these neurons can discriminate the exact goal location at the beginning of the journey. We discovered that, during navigation, a subset of CA1 neurons altered their firing rates depending on the future goal location while maintaining their spatial tuning (i.e. rate remapping). The dimensionality reduction analysis on ensemble activity of CA1 neurons revealed separately but parallelly evolving neural-activity dynamics as the animals ran along the same path but visited different goals. Consistent with these observations, we confirmed the accurate decoding of task episodes with different goals by using the activity of CA1 neurons. Notably, this decoding works not only in proximity to goal locations but across the entire duration of task episodes with a given goal combination. These observations together imply that hippocampal neuronal ensembles form discrete state representations corresponding to navigation episodes with a particular distribution of spatial goals, which may allow neural circuits to point to an expected future destination at the beginning of navigation.

Disclosures: Z. Golipour: None. **A.M. Lopez:** None. **H.T. Ito:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.01/TT2

Topic: H.10. Human Learning and Cognition

Title: Pupil linked arousal during early skill learning

Authors: *D. DASH[1], F. IWANE[1], R. SALAMANCA-GIRON[1], W. HAYWARD[1], H. SUGATA[1], V. AZZOLLINI[1], M. BÖNSTRUP[2], E. R. BUCH[1], L. G. COHEN[1];
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Abstract: Background. During procedural learning of a new motor skill, performance improves very rapidly (early learning) until it reaches near plateau levels (late learning). Prominent performance improvements during early learning develop predominantly during rest intervals (micro-offline gains) interspersed with practice, a form of rapid consolidation of skill. Fluctuations in pupil diameter (PD) inform on arousal states related to human cognition. Here, we geared to investigate pupil-related arousal during early skill learning. Methods. We measured PD in 24 participants performing a procedural motor learning task involving repeated typing of keypress sequences separated by intervals of rest. Performance improvements during early learning were evaluated and related with pupil diameter. We investigated the relationship between pupil diameter during practice and rest intervals of early learning and performance (correct sequence typing speed) improvements (micro-online and micro-offline gains respectively). Linear regression modelling and Pearson correlation measures were used to

perform the analyses. Results. Practice led to substantial performance improvement during the initial training trials (early learning), largely accounted for by micro-offline gains developing during the rest intervals. Subsequent practice elicited smaller additional gains (late learning). PD during practice was larger than during rest periods (1-tail paired *t*-test: $t = 13.38$, $p < 0.01$). During early learning, PD at rest was larger than pre-, post-training and late learning rest (multiple comparisons with 1-tail paired *t*-tests: $t > 1.8$, $p < 0.04$, FDR Corrected); and strongly related to micro-offline gains (linear regression: $R^2 = 0.64$; $p = 0.003$; Pearson correlation: $r = 0.8$). This relationship was stronger during early learning than during control rest periods (pre- and post-training rest) across individuals (Wilcoxon signed rank tests: early vs pre: $p < 0.003$; early vs post: $p < 0.027$). We also observed a strong correlation of pupil diameter during practice intervals with micro-online gains ($r = 0.71$) and skill ($r = -0.86$) only during early learning. Conclusions. These results are consistent with a higher level of arousal during early than late skill learning. Our next steps include evaluating the ability of pupil diameter to reflect neural replay bursts.

Disclosures: D. Dash: None. **F. Iwane:** None. **R. Salamanca-Giron:** None. **W. Hayward:** None. **H. Sugata:** None. **V. Azzollini:** None. **M. Bönstrup:** None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.02/TT3

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI Grant Number 22H03492

Title: Change in pupil diameter with motor adaptation of attentional reaction time

Authors: *R. HIRANO[1], T. KIZUKA[2], S. ONO[2];
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Abstract: The purpose of the current study was to clarify the change in pupil diameter with motor adaptation of attentional reaction time (RT) tasks. Pupil diameter has been shown to be an indicator of cognitive load (mental effort) in the central nervous system to task demands and difficulty. Here, we examined whether pupil diameter reflects changes in cognitive load associated with motor adaptation due to repetition of the task. Previous studies have reported that motor learning reduces the activity level of the cerebral cortex. Based on these findings, we hypothesized that adaptation to RT tasks would alter pupil diameter. Therefore, we evaluated changes in pupil diameter as the task progressed using an attentional RT task, which passively manipulates spatial attention by cueing. Twelve subjects performed the tasks. Visual stimuli were presented on a CRT monitor at a distance of 57 cm from the participants. During the trial,

the participants were instructed to fixation on the fixation cross presented in the center of the monitor. A red dot was presented as a pre-cue at 5°, 10°, or 15° to the left or right centered on the fixation cross, and then a green dot was presented as a response stimulus. We set three conditions: a valid condition in which the response stimulus was presented at the same position as the pre-cue, an invalid condition in which the response stimulus was presented at the position opposite to the pre-cue, and a neutral condition in which the pre-cue was presented in the center of the monitor regardless of the response position. The background color of the monitor consisted of three colors: the center part including the fixation cross was gray, and the left and right sides were white and black, respectively. When confirming whether spatial attention shifts by cueing altered pupil diameter, we observed that the pupil diameter was smaller when the pre-cue was presented on a white background. Our results showed that the RT and pupil diameter tended to decrease as adaptation progressed. A significant correlation was also observed between RT and pupil diameter. It has been suggested that motor adaptation increases dependency on the cerebellum and decreases activity levels in the cerebral cortex. The present study is the first study to assess the decrease in cognitive load of the cerebral cortex associated with motor adaptation from pupil diameter. Furthermore, our results showed that RTs were significantly shorter under the valid condition than the invalid condition. These results indicate that RT is shortened by both manipulations of attention by cueing and task habituation.

Disclosures: **R. Hirano:** None. **T. Kizuka:** None. **S. Ono:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR112.03/TT4

Topic: H.10. Human Learning and Cognition

Support: NSF Grant 2218406

Title: Parallel processes of habit formation and response speed improvement

Authors: *Y. DU, A. M. HAITH;
Johns Hopkins Univ., Baltimore, MD

Abstract: Previous research has demonstrated that habit emerges after extensive practice (> 1000 trials). In addition to rendering behavior habitual, practice also improves skill, leading to faster response speeds. Therefore, habit formation following extensive practice might also be attributable to experience performing the task at low response times. It is also intuitive that the ability to respond rapidly may be a key benefit and incentive for forming habits. It remains inconclusive how habit formation relates to response speed, however; specifically, whether habits are created purely through repetition, or as a result of response speeds attained during practice. To answer this question, we asked participants to practice a 4-element visuomotor mapping with constrained response speeds, controlled by a timed-response approach. For half of

the participants, the allowed response time was very short, at 400 ms, while for the other half, it was relatively long, at 800 ms. In addition, we varied the duration of practice across participants from 300 trials to 4000 trials. To compare the effect of these differing practice conditions on habit formation, we revised the required mapping after practice was complete and assessed whether participants would be able to flexibly act according to the revised mapping, or habitually persist with the originally practiced response. After only 300 trials of practice, participants became habitual and showed a similar likelihood of generating the original responses despite the allowed response time they experienced during practice. This likelihood of expressing habitual responses increased with more practice (e.g., 1000 and 4000 trials), but only if participants practiced the original mapping under the 400 ms response time condition. Using a computational model to dissect two possible factors that could affect the behavioral expression of habit, we found that habit strength - the probability of generating a response after it is habitually prepared - increased with practice regardless of the allowed response time during practice. However, only the 400-ms group improved response speed with practice, suggesting that their higher likelihood of habitual behavioral expression was due to faster response speed and not higher habit strength. In summary, we found that task repetition is critical to increase habit strength and the nature of practice influences response speed. Our results provide evidence suggesting that improvement of response speed and habit formation are distinct processes that occur in parallel through practice.

Disclosures: **Y. Du:** None. **A.M. Haith:** None.

Poster

PSTR112. Human Motor and Skill learning

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Title: What comes next? Response time is affected by misprediction in a stochastic game

Authors: P. R. CABRAL-PASSOS[1], J. E. GARCIA[2], A. GALVES[3], *C. VARGAS[4];
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Abstract: The conjecture that the human brain detects the statistical patterns in a sequence of events was approached with a new framework. The relationship between a sequence of events and the sequence of response times (RTs') acquired during the exposure to these events was modeled using sequences of random objects driven by a stochastic chain with memory of variable length. This approach provides evidence that the RTs' depend on the context, the smallest sequence of past events required to estimate the next event. Moreover, we show that the RTs' of some contexts change after prediction failures (PF). Twenty-two right-handed participants (14 females, 26±6 years) played the Goalkeeper Game (ethics approval: CAEE 58047016.6.10015261). As a goalkeeper, the participant must predict, at each trial in a sequence of 1000 kicks, if the penalty taker will kick left, center or right. The participant takes his/her time to decide and then presses the associated button. The RT corresponds to the time interval from a visual cue up to the button press. A context tree (CT) algorithm was used to estimate CTs' from the sequence of RTs'. The algorithm consists in (1) calculating the maximum admissible tree given the sequence of the penalty taker's choices. Then, (2) visiting each branch of the tree, which contains at least one pair of sequences of the same size that differ only by the leftmost choice and comparing the distribution of RTs' associated with each sequence to another sequence of the same branch. (3) If at least a pair of sequences presents different distributions of RTs', we conclude that the leftmost choice does not change the RTs' associated to the biggest common suffix of the sequences and we prune the branch, otherwise we keep it. Results show that the mode CT, obtained from the estimated tree of each participant, is the context tree used to generate the sequence of choices of the penalty taker. Furthermore, the distance between the tree estimated from the RTs' and the kicker's tree diminished from the 1st to the 2nd third of the experiment ($Z = 2.15$, $p < 0.02$). The RTs' of each participant and context were then divided in 2 sub-samples, after PFs' and after prediction successes (PS). PF and PS were referenced to the context in the penalty taker sequence that addresses non-null probability to more than one choice, since prediction errors in the others were rare. We found that the RTs' of two of the five contexts depended on the prediction results one step back in the sequence ($p = 2.1/105$; $p < 0.01$), and for one of the contexts, on predictions two steps back ($p < 0.01$). In summary, the distribution of RTs' associated with a stochastic sequence of events depends on both the contexts and the results of previous predictions.

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Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.05/TT6

Topic: H.10. Human Learning and Cognition

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ICREA, ICREA Academia 2018
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Title: Predictability modulates performance monitoring neurophysiological responses during rhythm synchronization and reproduction

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Abstract: Music is a pleasurable experience that involves learning to anticipate upcoming events. In the music production domain, auditory predictions are integrated with motor components. For this reason, performance monitoring is a key process to be able to play a rhythm or a melody. In this study, we analyzed how synchronization and reproduction of rhythms were modulated by the predictability of individual auditory notes.EEG was recorded from 74 healthy people. Participants had to tap nine different rhythms in a synchronization learning task that also included reproduction trials without sound. Each rhythm was repeated ten times and asynchrony (the difference between the real auditory intervals and the tapped ones) was used to assess the learning. Participants were randomly assigned to three groups. Each group was provided with images aid with different degree of information on the notes to be reproduced.Note-by-note asynchrony decreased across repetitions and was higher for less predictable events. Images providing information on the rhythms also reduced asynchrony. EEG analysis revealed response-locked Error Negativity and Error Positivity-like components. Overall, these performance monitoring responses increased their amplitude for higher IC notes during synchronization. In addition, reproduction sequences where no sound was present showed similar modulations for asynchrony and for the Error Positivity-like component, but no modulation was found for the Error Negativity-like component.These results show that predictability in rhythm synchronization and reproduction plays an important role in modulating performance monitoring components, being related to outcome predictions.

Disclosures: **M. Deosdad Diez:** None. **J. Marco-Pallares:** None.

Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.06/TT7

Topic: H.10. Human Learning and Cognition

Support: NS116883
NS105839

Title: Perturbation Variability Does Not Influence Implicit Sensorimotor Adaptation

Authors: *T. WANG[1], J. TSAY[2], G. AVRAHAM[2], S. ABRAM[2], R. IVRY[2];
[1]Univ. of California, Berkeley, BERKELEY, CA; [2]Univ. of California Berkeley, Albany, CA

Abstract: Humans have an incredible ability to adjust their behavior in the face of noisy environments. How environmental variability, or uncertainty, influences sensorimotor learning remains unclear, and in particular, how this might vary across different processes that contribute to learning. Here we focus on implicit adaptation, the process that uses movement error to keep the sensorimotor system exquisitely calibrated. On the one hand, this system has been described as a system that responds in an automatic and rigid manner, insensitive to environmental statistics. On the other hand, recent theoretical and empirical work has suggested that the sensitivity of the adaptation system is optimized by tracking environmental statistics. One major source of evidence for this "memory-of-error" (MoE) hypothesis is that learning appears to be markedly attenuated in the presence of variable perturbations compared to when the perturbation is fixed (Albert et al., NHB, 2021). In the current study, we re-examine how environmental variability influences implicit sensorimotor adaptation. As a starting point we note that the adaptation system corrects for errors of different magnitudes in a non-linear manner, increasing in a proportional manner in response to small errors and saturating in response to large errors. In a series of simulations, we show that high and low (or no) variance conditions differ in how they sample this motor correction function. These sampling differences are sufficient to explain the effect of perturbation variance without reference to an experience-dependent change in error sensitivity. Moreover, compared to the MoE model, an adaptation model this is insensitive to environmental statistics provides a better account of a number of phenomena in the adaptation literature. As a direct test, we conducted an experiment (n=40) in which we manipulated the distribution of errors experienced during training. Consistent with both models, a high variance condition resulted in lower adaptation when the error distributions were biased as in the Albert et al. study. However, learning was identical for high and low variance conditions when the bias in the error distributions was eliminated. Taken together, the theoretical and empirical results reported in our study show that there is no measurable effect of perturbation variance on implicit adaptation. As such, the results provide compelling evidence that this form of sensorimotor learning is rigid.

Disclosures: T. Wang: None. **J. Tsay:** None. **G. Avraham:** None. **S. Abram:** None. **R. Ivry:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RI is a co-founder with equity in Magnetic Tides, Inc..

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR112.07/TT8

Topic: H.10. Human Learning and Cognition

Support: Natural Sciences and Engineering Research Council of Canada (NSERC RGPIN-2019-04440, D.S.M.)

Title: The Effects of Auditory Consequences on Visuomotor Adaptation and Motor Memory

Authors: *G. MALAGON[1], D. S. MARIGOLD[2];
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Abstract: Humans have a remarkable ability to learn a wide range of motor behaviors and adapt them to different conditions. Motor learning involves rectifying movement errors and retaining corrected actions for future execution. Recent research indicates that experiencing balance-threatening physical consequences when making a movement error during adaptation can enhance motor memory. This is perhaps not surprising, as learning to avoid injury is critical for our survival and well-being. However, it remains unclear whether other forms of consequences can impact motor learning. Twenty participants adapted to a novel visuomotor mapping induced by prism lenses while performing a precision walking task that required them to walk and step to the center of a target projected on the ground. We randomly divided participants into two groups: an auditory consequence group and a control group. In the auditory consequence group (n=9), participants received an unexpected loud (85dB) sound if they missed the target. Participants in the control group (n=11) faced no consequences for a stepping error. We found that the auditory group adapted faster, as reflected by reduced early adaptation foot-placement error (mean of adaptation trials 2 - 8; t test, $p = 0.037$). To probe generalization, we used an interlimb transfer test (i.e., stepping to target with non-adapted foot) and obstacle-avoidance task performed without the prisms and compared performance to baseline. Both groups showed generalization in the interlimb test, but the auditory group showed greater generalization (Group x Phase interaction, $p = 4.0e\text{-}5$). Neither group showed generalization in the obstacle task. To assess consolidation, we introduced an opposite direction visuomotor mapping following initial adaptation and evaluated relearning one week later using the early adaptation measure. Both groups had reduced foot-placement error during the second testing session, reflecting consolidation (Session main effect: $p = 3.3e\text{-}6$). Although the auditory group had less foot-placement error in both testing sessions (Group main effect: $p = 0.031$), we found no Group x Session interaction ($p = 0.154$) suggestive of one group consolidating the motor memory more than the other. Overall, our preliminary findings suggest that auditory consequences could serve as a valuable tool for accelerating initial motor learning.

Disclosures: G. Malagon: None. **D.S. Marigold:** None.

Poster

PSTR112. Human Motor and Skill learning

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Topic: H.10. Human Learning and Cognition

Support: NIH Grant NS116883
NIH Grant NS105839

Title: An implicit re-aiming process in sensorimotor adaptation

Authors: *T. LAM[1], T. WANG[2], R. IVRY[3];
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Abstract: Sensorimotor adaptation theories distinguish between implicit and explicit processes, with the former using a sensory prediction error to recalibrate the sensorimotor map and the latter using task error to adjust an aiming strategy. Here we ask if the re-aiming process also involves an implicit process. Our motivation comes from reinforcement learning literature where the dynamics of choice behavior can arise implicitly as task outcomes update the value associated with stimulus-action options.
We used a visuomotor rotation task to explore this question. To eliminate implicit recalibration, endpoint feedback was delayed for 2s. In Exp 1, the feedback position was gradually rotated from the hand position, reaching 70° after 150 trials before ramping back down to 25° (1 target). With this type of perturbation, we expected participants to adopt and modify an explicit aiming strategy over the course of the block. To assess whether an implicit process also exists, the perturbation block was followed by a no-feedback block where participants were instructed to reach directly to the target, foregoing any aiming strategy used during the perturbation block. Participants did a good job in tracking the rotation with the mean hand angle shifted by 26° at the end of training. Interestingly, the hand angle remained shifted by 14.3±6.0° in the aftereffect block, suggesting that there might be a significant implicit component in aiming. Alternatively, this aftereffect could reflect use-dependent learning, a bias towards recently performed movements. To evaluate these hypotheses in Exp 2 (n=22), we included reaches to targets flanking the training location to assess generalization in the aftereffect block. The use-dependent hypothesis predicts that reaches to the flanking targets will shift in opposite directions, attracted to the direction of adapted movements. In contrast, the implicit aiming hypothesis predicts a consistent directional shift for all targets. The results were consistent with the latter, suggesting the aftereffect is not caused by use-dependent learning. In Exp 3, we tested individuals with cerebellar degeneration (CD) and age-matched controls (n=15/group). Both groups compensated for the gradual rotation and reached a similar level in late training (~20°). Moreover, the CD group demonstrated a similar aftereffect to the controls.
These results highlight a novel implicit learning process contributing to sensorimotor adaptation. This process does not require precise feedback timing, is not dependent on the cerebellum, and appears to be best conceptualized as contributing to action selection rather than movement execution.

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Poster

PSTR112. Human Motor and Skill learning

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Title: Leveraging VR and BCI to enhance working memory and motor learning

Authors: *G. SCHRIFT[1,2], S. LANDO[3], J. HERSZAGE[2], D. ABELES[3], R. LURIA[2,3], N. CENSOR[2,3];
[1]Tel Aviv Univ., Tel Aviv-Yafo, Israel; [2]Sagol Sch. of Neurosci., [3]Sch. of Psychological Sci., Tel Aviv Univ., Tel Aviv - Yafo, Israel

Abstract: Virtual reality (VR) offers a simulation of the real world, providing an immersive 1st person perspective of various experiences. As such, it provides an effective platform to investigate cognitive processes in ways that were previously not possible and may offer new possibilities for the enhancement of these processes. Here, we explore the enhancement of working memory and motor learning using VR and brain-computer interfaces (BCI), aiming to reveal the underlying mechanisms. First, we leveraged VR to implement a 3D version of the change detection visual working memory (VWM) task, commonly presented in 2D. Repeated measures ANOVA showed higher accuracy for 3D relative to 2D stimuli ($F_{1,22} = 7.38$, $P = 0.01$), suggesting that depth related cues can lead to enhancement of VWM. The underlying neural correlates for this enhancement are evaluated by measuring the common EEG marker of contralateral delay activity. Second, we examined VR enhancement of execution-free motor skill learning. Motor training without physical execution has gained considerable attention in recent years, with research exploring various strategies to enhance motor skill acquisition. Among these strategies, motor imagery (MI) and action observation (AO) were extensively studied, and their congruent combination (AO+MI) has shown promising results, pointing to a synergistic effect facilitating skill acquisition. Recent advances in VR technology have raised the possibility of embodied 1st person AO+MI, where individuals can observe a virtual representation of themselves performing the motor task. This immersive approach may facilitate learning due to greater activation and engagement of the neural networks involved, as implied by reports of elevated mu event-related desynchronization (ERD) during 1st person AO and greater cortical excitability during virtual hand embodiment. Indeed, results show that 1st person AO+MI training of a motor sequence in VR can lead to significant learning gains (mean learning gains 3.67 ± 1.33 sequences SE, $P = 0.02$), suggesting that embodiment may support execution-free motor skill learning. Similar AO+MI training is now combined with EEG-BCI to further augment these effects, training participants to control a VR supernumerary limb. Together, findings from both lines of research may support the development of new applications for cognitive and motor training and rehabilitation.

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Poster

PSTR112. Human Motor and Skill learning

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Support: Discovery support, NSERC

Title: Determination of a neurophysiological biomarker of Motor Learning

Authors: *M. HASSANZAHRAEE, T. WELSH, J. L. CHEN;
Univ. of Toronto, Toronto, ON, Canada

Abstract: Motor learning through physical practice (PP) induces long-term potentiation (LTP)-like plasticity, transiently reducing further LTP-like after-effects—a state known as occlusion. Previous studies suggest that motor learning through mental practice (MP) occurs to a lesser degree than PP, and activates similar brain regions as PP. However, it is unclear whether mental practice engages LTP-like plasticity and, thus, an occlusion state. Aim 1 was to replicate prior work on PP and occlusion. We hypothesized that individuals in the PP group who demonstrate more occlusion will also demonstrate more learning on a motor task. Aim 2 is novel and evaluates mechanisms that underlie MP. We hypothesized that the MP group would exhibit some occlusion relative to a control group that does not learn the motor task, but would exhibit less occlusion than the PP group. The sample size is 30; data collection is ongoing and results of 21 neurotypical individuals are presented here: PP (4 male/3 female, mean age 27.3 (9.6)), MP (3 male/4 female, mean age 22.6 (2.7)), and control (4 male/3 female, mean age 21.6 (22.6)) groups. On Day 1, TMS was applied to left primary motor cortex before and after tDCS (immediately and 15 min later). tDCS was applied (1mA, 7 min, 25cm^2 electrodes in sponges) with the anode on C3 and cathode on Fp2. On Day 2, participants performed the Sequential Visuomotor Isometric Pinch Task (SVIPT) across 8 blocks (1 block=15 trials), followed by TMS before and after tDCS. On Day 3, one block of the SVIPT was performed to assess motor skill retention, an indicator of learning. Outcome measures were: 1) Skill: a measure that quantifies learning by accounting for speed and accuracy; 2) Occlusion index (OI): as assessed with the TMS-motor evoked potential (MEP) before (pre) and after (post) tDCS. The amount of occlusion was calculated as $[postMEP/preMEP]_{Day1}$-$[postMEP/preMEP]_{Day2}$. Results from one-way ANOVAs showed that the PP group experienced a greater amount of learning ($F(2,20)= 4.19$, $p= 0.03$) and have a higher OI (($F(2, 20) = 16.53$, $p < 0.01$) compared to the MP and control groups. There was a positive correlation between learning and the OI ($r = 0.79$, $p = 0.032$). These findings show that more occlusion is associated with more learning. The MP group showed intermediate amounts of learning and occlusion relative to the PP and control groups. Therefore, MP may lead to similar neuroplastic changes, though not to the same extent as with PP, and OI may be used as a potential biomarker to predict the level of learning.

Disclosures: M. Hassanzahraee: None. **T. Welsh:** None. **J.L. Chen:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.11/TT12

Topic: H.10. Human Learning and Cognition

Support: NIH/NIA R01-AG071585

Title: Does context change the effect of pain on retention of locomotor learning?

Authors: *S. R. JACKSON, J. M. WOOD, S. M. MORTON;
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Abstract: The effect of pain on motor learning and retention is not well understood, which could have important consequences for patients undergoing rehabilitation. Our group and others have shown that pain could interfere with retention of motor learning. However, some evidence suggests this effect may not be truly due to pain, but due to the effect of a context change from learning (in a painful state) to retention testing (in a nonpainful state). Yet retention with and without a context change has not been directly compared. Therefore, we examined the effect of pain on locomotor learning and retention, specifically the effect of a context change between learning and retention conditions, on the magnitude of retention. Three groups of young healthy adults performed a locomotor learning task: a 'no pain' group received no intervention; a 'pain during learning' group received a painful stimulus during Day 1 learning; and a 'pain during learning and retention' group received the same painful stimulus during both Day 1 learning and Day 2 retention testing. Pain was induced via topical capsaicin (0.1%) and heat applied to the low back. On Day 1, all participants learned a new asymmetric stepping pattern using visual feedback. A monitor displayed real-time feedback of step lengths, represented as bars growing vertically on the screen. During learning, the feedback was distorted, making one leg appear to take longer steps and the other to take shorter steps. To hit the visual step length targets, participants had to acquire a novel step asymmetry of 12%. Twenty-four hours later, retention was tested in two different ways; uncued, i.e., without visual feedback and cued, i.e., with visual feedback. Force plates and a 3D motion capture system recorded gait events and measured step lengths, respectively. Thus far, preliminary data indicate there are no differences in learning between groups, consistent with our prior work. However, retention levels appear to differ among groups. Interestingly, the context effect may vary based on whether retention is tested in cued or uncued conditions. These findings provide evidence that acquisition of a new motor skill is possible for individuals experiencing pain and suggest that context may affect some aspects of retention.

Disclosures: S.R. Jackson: None. **J.M. Wood:** None. **S.M. Morton:** None.

Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.12/TT13

Topic: H.10. Human Learning and Cognition

Support: RNUDS (DSTG) Research Agreement 9208

Title: Mindfulness as a cognitive training technique: an investigation of dynamic contexts, individual factors and resting-state EEG.

Authors: *C. A. DZIEGO[1], I. BORNKESSEL-SCHLESEWSKY[1], M. SCHLESEWSKY[1], R. SINHA[2], M. A. IMMINK[3], Z. R. CROSS[4];
[1]Cognitive Neurosci. Lab., Univ. of South Australia, Magill, Australia; [2]Ctr. for Workplace Excellence, Univ. of South Australia, Adelaide, Australia; [3]Sport, Health, Activity, Performance and Exercise (SHAPE) Res. Ctr., Flinders Univ., Adelaide, Australia; [4]Northwestern Univ., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Mindfulness practices are typically used in Western contexts to enhance psychological wellbeing and emotional regulation. Recent research, however, is highlighting how mindfulness can further enhance global attentional capacity, working memory and motor performance. The current study aimed to investigate if engagement in a mindfulness training program augments performance in dynamic, complex settings, and how individual resting-state electrophysiology may be associated with these changes. Participants (n = 40) completed two in-lab experimental sessions involving the Control-Room-Use-Simulation Environment - a dual-screen simulation where participants act as a submarine's Target Motion Analyst (TMA) - with resting-state EEG recorded. Between sessions, participants engaged in one-week of at-home cognitive training (based on mindfulness techniques) guided by audio recordings. Linear mixed-effect regressions revealed that increased engagement in the mindfulness-based training regime (ranging from 0-21 sessions) was associated with improved performance in the second testing session of the TMA task, even when controlling for baseline performance. Further analyses demonstrated that this effect remained relatively consistent across participants' resting-state EEG activity (i.e., individual alpha frequency and 1/f activity), personality measures, enjoyment ratings and timing of intervention adherence. Our results thus indicate that mindfulness-based cognitive training leads to performance enhancements in distantly related tasks, irrespective of individual differences in information processing, as measured by resting-state EEG. Nevertheless, we did observe that nuances in the magnitude of cognitive enhancements were contingent on the timing of adherence, regardless of total volume. Overall, our findings suggest that mindfulness-based training could be used in a variety of settings to enhance distantly related performance outcomes.

Disclosures: C.A. Dziego: None. **I. Bornkessel-Schlesewsky:** A. Employment/Salary (full or part-time):; University of South Australia. 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.; Defence Science and Technology Group (Research Network for Undersea Decision Superiority). Other; Australian Research Council Future Fellowship. **M. Schlesewsky:** A. Employment/Salary (full or part-time):; University of South Australia. 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.; Defence Science and Technology Group (Research Network for Undersea Decision Superiority). **R. Sinha:** A. Employment/Salary (full or part-time):; University of South Australia. 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.; Defence Science and Technology Group (Research Network for Undersea Decision Superiority). **M.A. Immink:** A. Employment/Salary (full or part-time):; Flinders 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.; Defence Science and Technology Group (Research Network for Undersea Decision Superiority). **Z.R. Cross:** A. Employment/Salary (full or part-time):; Northwestern Feinberg School of Medicine.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.13/TT14

Topic: H.10. Human Learning and Cognition

Title: Neural correlates of singing production: A systematic review and ALE meta-analysis of neuroimaging studies

Authors: *T. B. M. RUBAT DU MÉRAC[1,3,4], Y. N. MEKKI[1,4], R. L. GORDON[1,4,5,2,6];
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Abstract: Human singing is a universal and multifaceted skill, presumably supported by an intricate neural network. We performed a systematic review and activation likelihood estimation (ALE) meta-analysis on PubMed records following the PRISMA guidelines (Page et al., 2021). 9 task-based neuroimaging studies (218 foci singing production vs. rest contrasts, 143 subjects) covering: overt pitch-singing, (non) lyrical singing, and covert singing were included. Results showed 51 activations (p &lt 0.05, family-wise error rate corrected) including on the perisylvian, limbic areas and cerebellum. More specifically, bilateral activations were observed on the premotor and supplementary motor areas, posterior superior temporal gyrus, primary auditory cortex (PAC), supramarginal gyrus, Broca's area pars opercularis, as well as on the limbic system (cingulum, insula). Left-lateralization was captured for the primary motor cortex, angular gyrus, middle temporal gyrus and the cerebellum (VI, vermis VII, crus I and II), while right-lateralization was observed for Broca's area pars triangularis, the planum polare (PP), amygdala, thalamus, and pallidum. Activations were consistent with prior findings (Brown et al. 2009). We additionally observed right lateralized signal on the amygdala, cingulum, PAC, pallidum and PP,

thus confirming the previously established increased involvement of the right cortical hemisphere in singing (Riecker et al., 2000). Our reported bilateral activation of the insula was not reflected in a previous meta-analysis of syllable-singing (Brown et al., 2009), despite the known involvement of the left insula in speech (Ackermann & Riecker, 2004). The right insula, however, has been thought to take part in experience-dependent modulation of sensorimotor feedback during vocal motor control tasks (Kleber et al., 2013), and its impairment has previously been associated with vocal amusia (Terao et al., 2006). Ultimately, and given the observed left cerebellum projections to the right cerebral cortex (Palesi et al., 2015), showing greater involvement in singing (Riecker et al., 2000), the strong observed lateralization of the left cerebellum confirms previous findings on its relevance to singing (Callan et al., 2006). This suggests a more specific role in complex singing for such non-overlapping regions, as compared to a previous ALE meta-analysis targeting syllable-singing, improving our current understanding of the singing network. Future meta-analyses of singing contrasted with higher-level contrasts will help validating our findings and assess their degree of specificity to singing production.

Disclosures: T.B.M. Rubat du Mérac: None. **Y.N. Mekki:** None. **R.L. Gordon:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

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Program #/Poster #: PSTR112.14/TT16

Topic: H.10. Human Learning and Cognition

Support: NSERC 2021-04026
NSERC CREATE Complex Dynamics of Brain & Behaviour Training Grant

Title: Effects of emotional arousal on motor learning in musical contexts

Authors: *A. W. ALBURY[1], R. BIANCO[2], A. P. JOHNSON[1], V. B. PENHUNE[1];
[1]Psychology, Concordia Univ., Montréal, QC, Canada; [2]Italian Inst. of Technol., Rome, Italy

Abstract: Musical reward is known to induce dopaminergic activation in common reward circuits in the striatum. Additionally, musical reward and performance recruit motor areas involved in coordination of movements. Musical reward is believed to rely heavily on prediction errors which are responsive to context predictability. Musical predictability influences reward such that moderately predictable music is preferred over highly predictable or overly complex music, resulting in an inverted U-shaped relationship between liking and predictability. Given that reward value can affect motor learning and that prediction plays a role in motor planning during music performance, it's possible that predictability and reward interact to influence motor learning. To test this interaction, we developed a paradigm in which non-musicians learn to play melodies that vary in their level of predictability and by extension, induced reward. We then examined the learning rate of these melodies and measured hedonic response to them using

pupillometry and subjective ratings of enjoyment. Stimuli consisted of 16 isochronous and monophonic melodies that were 13 notes long. Melodies were constructed to elicit a range of liking responses, and so that the first 9 notes varied in predictability, but the last 4 notes were similar in predictability. This ensured that the motor requirements of the 4 notes that participants learned to play were consistent across stimuli. Note predictability was calculated using an information theoretic model of music trained on a corpus of Western music. Participants listened to the melodies while pupil dilation was recorded and gave subjective ratings of how much they liked each melody. Following this, participants completed a piano task in which they learned to finish the melodies by playing the endings. Learning was assessed via accuracy and asynchrony of keypresses across trials. We found that participants successfully learned the melodies, displaying decreased asynchrony as trials progressed. We also found minimal influence of subjective liking ratings on motor performance, however there was a significant interaction between liking ratings and melody predictability. The observed effect of melody predictability on motor learning despite played notes having similar predictability levels demonstrates that learning is affected not only by objective characteristics of music the music being performed but also prior context.

Disclosures: A.W. Albury: None. **R. Bianco:** None. **A.P. Johnson:** None. **V.B. Penhune:** None.

Poster

PSTR112. Human Motor and Skill learning

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.15/TT17

Topic: H.10. Human Learning and Cognition

Support: NSF 2050833

Title: Neural Mechanisms of Rule-Based Category Learning in Humans

Authors: *A. THOKSAKIS, E. ESTER;
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Abstract: Categorization allows humans to assign unique and behaviorally relevant labels to sensory stimuli. To study this process, researchers usually train volunteers to classify novel stimuli into different groups based on an arbitrary boundary. Critically, there are at least two strategies that participants could use to solve these tasks. On the one hand, participants could rely on associative learning by storing stimulus-response associations across the range of to-be-categorized exemplars. On the other hand, participants s could pursue a rule-based strategy that entails learning the category-defining boundary and comparing to-be-classified exemplars against an internal representation of this boundary. Here, we evaluated this possibility. We recorded EEG while human participants learned to classify a set of continuously varying orientated stimuli into discrete groups. We reasoned that if participants pursued a rule-based

categorization strategy then the amplitudes of EEG signals associated with sensory decision making should scale with angular distance separating a to-be-categorized exemplar from the category-defining boundary. This is precisely what we found: the amplitude of the centro-parietal positivity (CPP), an event-related potential previously linked with sensory decision making, reached a peak amplitude immediately before participants' overt category judgments, and the amplitude of this component scaled inversely with the angular separation between to-be-categorized exemplars and the category-defining boundary. This suggests that participants categorized stimuli by sampling sensory evidence from to-be-categorized exemplars and comparing this evidence against an internal representation of the category-defining boundary. More generally, the results suggest that human categorization can be understood using the same conceptual frameworks that have been used to characterize sensory decision making in other contexts.

Disclosures: A. Thoksakis: None. **E. Ester:** None.

Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.16/TT18

Topic: H.10. Human Learning and Cognition

Support: Robotics and AI for Socio-economic Empowerment (RAISE), NextGenerationEU

Title: Human-human sensorimotor interaction as a game: partner representatons and game theory to model the development of interpersonal coordination

Authors: C. DE VICARIIS, L. BANDINI, *V. SANGUINETI;
Informatics, Bioengineering, Robotics, Systems Engin., Univ. of Genoa, Genoa, Italy

Abstract: Human dyads develop coordination strategies that can be interpreted as Nash equilibria. However, convergence depends on uncertainty about the partner actions. This has suggested that action selection is based on an explicit representation of what the partner will be doing (partner model). However, the mechanisms underlying the development of a joint coordination over repeated trials remain unknown. Here we present a general modeling framework - based on game theory and Bayesian estimation - to understand how joint coordination develops over repeated trials. Joint tasks are modeled as mixtures of quadratic games, in which each participant's goal is described by a set of quadratic cost functions. Action selection is based on stochastic optimization of its expected cost given the partner model prediction, which optimally combines predictions and sensory observations.The model can be used to simulate interactive behaviors, thus helping to make specific predictions; and to analyze the action time series in actual joint action experiments, thus providing quantitative metrics to describe individual interaction behaviors. The model reproduces well the temporal evolution of

performance observed in continuous sensorimotor versions of classical discrete games like the Prisoner's Dilemma (PD) or Stag Hunt (SH), and how performance is affected by manipulating the available information about the partner. In a spatial variant of the SH game, the model predicts that different representations of the partner lead to different Nash equilibria. In different variants of a joint two via-point game, the model captures well the temporal evolution of performance. The model is also capable of estimating individual model parameters from the action time series in actual joint action experiments, thus allowing to characterize the behaviors of individual dyad participants. The modeling framework also suggests a general methodology to translate classical discrete games into continuous sensorimotor games, so that not only the cost structure but also the Nash equilibria are preserved. This allows to further test whether game theory is a valid extension of motor control theories to interactive settings.Computational models of joint action may help identifying the factors preventing or facilitating the development of coordination. Models can be used in clinical settings, to interpret the observed behaviors in individuals with impaired interaction capabilities. Finally, they provide a theoretical basis to devise artificial agents with an ability to establish forms of coordination that facilitate neuromotor recovery.

Disclosures: **C. De Vicariis:** None. **L. Bandini:** None. **V. Sanguineti:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.17/TT19

Topic: H.10. Human Learning and Cognition

Title: Compression of hierarchical cognitive representations with extensive practice

Authors: *T. A. ADANRI[1], J. E. TRACH[2], S. D. MCDOUGLE[2];
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Abstract: People often form hierarchical representations of tasks while learning, even when hierarchical structures are not required. However, previous work has found that structure learning is behaviorally costly. In the present study, we examine cognitive representations of visuomotor mapping changes as expertise is gained by analyzing patterns in reaction times and using computational models to formalize individual behavior. Specifically, we ask how extensive practice changes the structure of cognitive representation in decision making tasks. We had participants (N=18) learn eight stimulus-response associations with a latent hierarchical structure, via reinforcing reward feedback. Across eight days of training, participants completed over 2,000 trials of practice with the visuomotor mapping. We also aimed to characterize the dynamics of cognitive and motor processing while executing hierarchical decisions at the individual decision level. Participants also completed two forced-response-time tasks on day one and day eight, where we manipulated the allotted preparation time before each response. We find evidence of a change in representation with expertise; specifically, there is a change in the speed

and pattern of reaction times from day one to day eight such that there appears to be a "flattening" of the mental representation. Further, the best model for participant behavior showed decisions were made working from the top of the hierarchy to the bottom on day one, but by day eight this model was no longer the best fit. These results indicate that there is some compressing of mental representation structures as expertise is gained. Overall, this work contributes to our understanding of hierarchical decision making's dynamics and interactions between cognitive systems during decision making, and makes specific neural predictions for hierarchical action selection.

Disclosures: T.A. Adanri: None. **J.E. Trach:** None. **S.D. McDougle:** None.

Poster

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CAS Project for Young Scientists in Basic Research Grant No.YSBR-071

Title: Long term motor experience modifying neural representations of action observation in parietal cortex

Authors: *H. HE[1], Y. GE[3], Z. LIU[4], S. HE[2], J. ZHANG[4];
[2]Inst. of Biophysics, [1]Chinese Acad. of Sci., Beijing, China; [3]Inst. of Biophysics, Chinese Acad. of Sci., Beijing, China; [4]Inst. of Biophysics, Chinese Acad. of Sci., Beijing, China

Abstract: Long-term motor experience, such as sports training, not only modulates the neural representations in the motor cortex, but also enhances the neural responses elicited by associated action observation in the fronto-parietal cortex. However, the mechanism of such altered neural responses in the fronto-parietal cortex is unclear. Whether and how does the motor training modulate the neural representations of action observation? Here, we used fMRI to directly compare the neural response patterns elicited by action observation of table tennis in athletes (n=14, 2 females, age 18-24), amateurs (n=14, 3 females, age 19-27), and novices (n=14, 8 females, age 19-28). The results showed higher decoding accuracies for different table tennis actions in the athletes than in the other groups, and such an improvement was not observed for other everyday actions, suggesting an improved sensitivity of neural representations to trained actions in the parietal cortex. In addition, using the "hyperalignment" method, impaired decoding performance was observed when the decoder was trained and tested with individuals from different groups. Furthermore, the neural response patterns in the parietal cortex could be used to

classify the athletes from the non-athlete groups. Our results show that the long-term motor training not only increases the sensitivity of the neural responses during action observation, but also modifies the neural representations in the parietal cortex. These altered neural representations could potentially be part of the mechanisms supporting the understanding of others' actions in sports competition.

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Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.19/TT21

Topic: H.10. Human Learning and Cognition

Support: NSERC Discovery Grant

Title: Long-term effects of concussion on sensory gating, attention, and motor learning

Authors: *K. WALACH-GOSSE, R. S. STAINES, K. E. BROWN, S. K. MEEHAN, W. R. STAINES;
Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Motor learning relies on the sensorimotor system to interpret, adapt, and integrate sensory inputs to guide motor behavior. A key tenet of the somatosensory system is the ability to selectively facilitate or inhibit incoming afferents based on task relevancy (sensory gating). Sensory gating occurs at early cortical processing stages and has been shown to be impacted in individuals with a history of concussion. Past work from our lab found a delay in relevancy-based facilitation in a group with a history of concussion compared to healthy controls. The current work aimed to understand the behavioral manifestations that result from disruptions to relevancy-based gating modulations at early cortical processing stages in the concussion population. A total of 40 participants were recruited to participate in this study with 25 in the concussion history group (Hx) and 15 in the control group (No-Hx). This study consisted of 2 experimental sessions that occurred 24 hours apart. During session 1, somatosensory-evoked potentials (SEPs) were elicited via median nerve stimulation while subjects performed a task that manipulated their focus of attention toward or away from proprioceptive feedback. Subjects then completed an implicit motor sequence learning task relying solely on proprioceptive cues. Individuals performed a retention test at session 2, followed by a visual attentional blink (AB) task. The AB is a phenomenon elicited by the rapid presentation of sequential targets which results in reduced accuracy of detecting the second target at the expense of detecting the first target. The No-Hx performed the implicit learning task at session 1 and a retention test at session 2 because SEP and AB data were compared to control data previously collected by this lab. SEP data replicated past work showing an absence of relevancy-based facilitation at early cortical processing stages (N20-P27) that emerged at later processing stages. Our Hx showed evidence of

relevancy-based facilitation at either the P50-N70 or the N70-P100 consistent with past work that found this to occur at the N70-P100. Performance on the learning task was not significantly different between the Hx and No-Hx. Performance on the AB task revealed greater AB magnitude in the Hx compared to the No-Hx. Collectively, these results suggest a compensatory strategy in the Hx that enables them to learn to the same degree as No-Hx. However, when the attentional system is taxed with high temporal demands, there are decrements in the Hx performance. These results are of particular importance given that these individuals are at an increased risk of sustaining subsequent concussions, and musculoskeletal injuries.

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Poster

PSTR112. Human Motor and Skill learning

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Topic: H.10. Human Learning and Cognition

Support: This research was supported by the Intramural Research Program of the NIH.

Title: Crowdsourced evaluation of the relationship between age and early procedural skill learning

Authors: *W. HAYWARD, E. BUCH, F. IWANE, V. AZZOLLINI, H. SUGATA, D. DASH, R. F. SALAMANCA-GIRON, L. G. COHEN;
NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD

Abstract: Background: Previous work documented age-related differences between young and elderly subjects in procedural skill learning over days (Maceira-Elvira et al. 2022). Interestingly, most performance improvements develop during the rest periods during initial practice trials of early learning (micro-offline (Bönstrup et al. 2019)). Previous work showed that use-dependent plasticity in the motor cortex drops after age 50yo (Sawaki et al. 2003). Here, we investigated early learning across the life span in an online study involving 392 healthy right-handed adults (age 18-78 years). **Methods**: Healthy volunteers performed a well-characterized motor sequence typing task alternating 10-second practice with 10-second rest for 36 trials over 12 minutes (Bönstrup et al. 2019; Bönstrup et al. 2020). We measured performance improvements during practice (micro-online) and rest (micro-offline) intervals and total early learning (defined as the period during which performance reaches 95% performance of total skill during the practice session). Subjects were recruited using an online crowdsourcing tool (Prolific.co). **Results**: Across all ages we found an inverse relationship in which subjects with most prominent micro-offline gains had less micro-online gains during early learning. Results across different age bins are presented and compared. We provide large-scale data on the relationship between age, sex

and microlearning in this group of 392 subjects. One area of interest was the ability to characterize age influences on micro-offline learning, a form of rapid consolidation. Preliminary results indicate that micro-offline learning remains present across the life span **Conclusion:** Microscale offline gains contribution to early learning is not limited to the young but is present in elderly human subjects learning a novel procedural skill task.

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Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.21/TT23

Topic: H.10. Human Learning and Cognition

Title: Increased duration of practice-induced motor memory reactivation does not benefit retention or transfer of an upper extremity motor skill in healthy older adults

Authors: *K. TOMLIN[1], ***K. B. TOMLIN**[2];
[1]Univ. of Maryland, Sch. of Med., Baltimore, MD; [2]Univ. of Maryland, Sch. of Med., Ellicott City, MD

Abstract: Purpose Practicing a learned motor skill can strengthen the associated motor memory through the processes of memory reactivation and reconsolidation. We previously showed that fewer rather than more repetitions of a complex motor task can enhance contralateral transfer of task performance in healthy younger, but not older, adults. One possible explanation for this age-related difference is impaired acquisition of the complex motor skill by older adults in the two-week training period. Here, healthy older adults' retention and intermanual transfer of a complex motor task are compared between two-week and four-week practice durations in brief and long task reactivation groups. We hypothesized that an increased duration of practice would benefit retention and intermanual transfer of the motor skill. **Subjects** 40 older adults between 65 and 84 years old participated in the main study. Subjects had clear right hand dominance and computer access. 10 older adults completed two-weeks of additional practice.**Methods** Healthy older adults practiced a virtual star tracing task during seven visits within a two-week period. Subjects performed either three trials (brief reactivation group) or ten trials (long reactivation group) per session using their left, non-dominant hand. Retention and intermanual transfer were tested at two-week follow up. A sub-sample was then selected, evenly from brief and long reactivation groups, to complete an additional two-weeks of motor practice. Retention and transfer were re-assessed at four-week follow up. Outcomes of interest included speed, accuracy, and skill as defined by a speed-accuracy tradeoff function.
Results Regardless of group, subjects demonstrated significant improvements on the trained task between baseline and two-week follow up ($p < 0.05$); however, no significant between-group differences in retention or transfer skill were identified. Between two-week and four-week

practice timepoints, both brief and long reactivation groups demonstrated small, non-significant, improvements in skill on the trained (left) upper extremity. Between two-week and four-week practice timepoints performance on the untrained (right) upper extremity did not significantly change in either reactivation group.
Conclusions Extending the duration of motor memory reactivation in healthy older adults, from a two week to a four week period, does not appear sufficient to elicit the intriguing transfer benefit from brief practice shown in healthy younger populations. Future research should investigate methods to optimize complex skill transfer in older adults.

Disclosures: K. Tomlin: None. **K.B. Tomlin:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.22/TT24

Topic: H.10. Human Learning and Cognition

Title: Combination of individualized oscillatory tDCS and electrical noise stimulation can facilitate corticomuscular coherence and motor skill acquisition in healthy individuals

Authors: *D. KUDO[1,2], T. KOSEKI[1], K. YOSHIDA[1], K. TAKANO[4], T. SATO[4], N. KATAGIRI[4], M. NITO[3], S. TANABE[5], T. YAMAGUCHI[6];
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Abstract: Functional beta oscillatory coupling between the primary motor cortex and spinal motor neurons plays a vital role in motor learning (Yamaguchi et al., 2020). We have reported that oscillatory transcranial direct current stimulation (otDCS) with individualized frequencies of corticomuscular coherence (CMC) immediately enhances CMC amplitudes; however, the enhancement is only short-lived (Kudo et al., 2022). The sensory input of electrical noise stimulation (ENS) may promote the enhancement of CMC induced by otDCS via stochastic resonance (Moss et al., 2004). Therefore, we investigated the effects of otDCS combined with ENS on CMC and motor acquisition in healthy individuals. In experiment 1, 19 young and healthy volunteers participated in a single-masked, sham-controlled, crossover study. All participants randomly received the following three interventions for 10 min each on different days: otDCS combined with ENS, otDCS combined with sham ENS, and sham otDCS combined with ENS. otDCS electrodes were positioned over the vertex (Cz) and forehead. ENS was delivered to the right common peroneal nerve. CMC between the Cz and tibialis anterior muscle was assessed for 2 min of tonic dorsiflexion before (Pre), immediately after (T0), 10 min after

(T10), and 20 min (T20) after the stimulation. In experiment 2, 54 young and healthy volunteers participated in a single-masked, sham-controlled, randomized study. Participants were categorized on the basis of sex and randomly added to three groups: otDCS combined with ENS, otDCS combined with sham ENS, or sham otDCS combined with sham ENS. Participants performed visuomotor practice involving accuracy tracking with rapid shifts in ankle dorsiflexion force levels. In experiment 1, otDCS combined with ENS significantly increased CMC at T0 ($P < 0.01$) and T10 ($P < 0.05$) compared with CMC at Pre. However, the increase in CMC was only observed immediately after otDCS was combined with sham ENS ($P < 0.01$). In experiment 2, otDCS combined with ENS significantly improved motor acquisition compared with sham otDCS combined with sham ENS ($P < 0.05$). These findings suggest that individualized beta-band otDCS combined with ENS facilitates corticomuscular coherence and motor acquisition in healthy individuals.

Disclosures: D. Kudo: None. **T. Koseki:** None. **K. Yoshida:** None. **K. Takano:** None. **T. Sato:** None. **N. Katagiri:** None. **M. Nito:** None. **S. Tanabe:** None. **T. Yamaguchi:** None.

Poster

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Topic: H.10. Human Learning and Cognition

Support: This study was conducted as part of Global Singularity Research Program for 2023 financially supported by KAIST.
This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) and funded by the Korean government (MSIT) [NRF2019M3E5D2A01066265].

Title: The Role of Representational Capacity in Strategic Learning and Generalization Abilities: Structural MRI Evidence from Sensorimotor Adaptation Experiments

Authors: *Y. SONG[1], P.-S. KIM[1], S. JANG[1], J. D. KRALIK[2], J. JEONG[2];
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Abstract: Sensorimotor learning (SL) in the brain is notable for its use of “cognitive strategies” and the “generalization” of prior knowledge. Previous studies indicate that both processes are partly attributed to the brain's capacity for representation. However, the neural principles underpinning those processes are yet to be fully understood, leading to the focus of the current study. Our theoretical investigations based on a probabilistic framework indicated that representational capacity (RC), the number of representations encodable in a specific area, could affect strategic learning and generalization abilities. Building upon the premise that regional grey matter volume (GMV) may reflect a specific area's RC, we hypothesized that strategic learning

and generalization abilities might be associated with GMV. To examine this, we conducted two sensorimotor adaptation experiments, quantifying each participant's regional GMV using voxel-based morphometry from MRI structural data. In the first experiment (n=47, female=22, mean age=23.7, s.d.=2.6), participants adapted to erase given stimuli using a horizontally reversed computer mouse (i.e., mirror erasing). We found that the initial (strategic) increase in adaptation ability positively correlated with the cerebellum's GMV and negatively correlated with the frontal lobe ($p_{FWE}<0.05$). Additionally, rapid restoration tendencies of not-mirrored erasing (speculated as a strategic response to aftereffects) positively correlated with the caudate nucleus's GMV ($p_{FWE}<0.05$). These findings provide neural evidence for a close association between RC and strategic SL ability. The second experiment (n=48, female=24, mean age=24.3, s.d.=2.4) required participants to generalize their mirror-erasing skills from a simple shape (i.e., a square) to a more complex one (i.e., a cursive 'y'). Findings indicated a negative correlation between generalization amount and the GMV of the cerebellum and putamen, while positively correlating with multiple cerebral areas, including the frontal, parietal, and occipital lobes ($p_{FWE}<0.05$). Notably, GMV had predictive capacity for future generalization amounts, indicating that RC in various areas also influences the complexity of the SL process, potentially leading to overfitting. Our theoretical framework further provides a technical tool to specify connections that are adjusted during sensorimotor learning from those structural results, suggesting the crucial role of connectivity changes from the frontal lobe to the cerebellum for rapid SL. By highlighting the concept of RC, our study lays the basis for understanding the brain's notable SL capabilities.

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Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.24/TT26

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI 20KK0369

Title: Caudate connectivity parallels rapid consolidation of skil

Authors: *H. SUGATA[1,2], F. IWANE[2], W. HAYWARD[2], V. AZZOLLINI[2], D. DASH[2], R. SALAMANCA-GIRON[2], M. BÖNSTRUP[3], E. R. BUCH[2], L. G. COHEN[2];
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Abstract: Background: Early learning of a new skill results in rapid performance gains that develop during rest intervals of practice (micro-offline gains). This form of rapid consolidation engages the hippocampus. However, complex cognitive processes like motor learning rely on

wider oscillatory activity over distributed brain networks. Here, we evaluated network-level brain oscillatory connectivity linked to micro-offline gains during early procedural skill learning. **Methods:** 31 subjects practiced typing a 5-item numeric sequence (i.e., 4-1-3-2-4) repetitively as fast and accurately as possible with the left non-dominant hand. MEG was continuously recorded from 271 sensors (CTF 275 MEG system). Training consisted of 36 practice trials of 10 s and was interleaved with rest periods of 10 s. Skill was measured as the correct sequence typing speed. Micro-online, micro-offline, and total early learning were determined. First, we performed an exploratory analysis to identify the optimal MEG functional connectivity frequencies (1-50Hz) linked to early learning. We then calculated the number of connections of individual brain regions (i.e., degree of connectivity [DC]) during pre-training rest, practice, and inter-practice rest periods using the optimal functional connectivity frequencies. Then we performed a correlational analysis between DC and learning. **Results:** Skill improved rapidly during early learning. Low beta was the optimal MEG functional connectivity frequency linked to early learning. Micro-offline gains correlated with DC in the bilateral caudate nucleus (right, Pearson's $r = 0.553$, $p = 0.0013$; left, Pearson's $r = 0.444$, $p = 0.0124$), and the right putamen (Pearson's $r = 0.4736$, $p = 0.0071$). **Conclusions:** These results document a strong relationship between brain oscillatory connectivity in the low beta range centered in regions of the human striatum and this form of rapid consolidation of a skill.

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Poster

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Program #/Poster #: PSTR112.25/TT27

Topic: H.10. Human Learning and Cognition

Support: the National Research Foundation of Korea (NRF-2021R1A2C2011648)
Hanyang University (HY-202000000002753)
Center for Neuroscience Imaging Research, Institute for Basic Science, Korea (IBS-R015-D1)

Title: Cortico-hippocampal representational similarity during wakeful rest supports rapid consolidation of human motor skill learning

Authors: *S. YOON[1], S. KIM[1,2];
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Abstract: Cortico-hippocampal interaction is widely recognized as integral to the memory consolidation during sleep or wakeful rest. However, the extent of its engagement in non-

declarative motor memory during skill learning remains largely undefined. Specifically, it remains unclear how neural representations in cortical and hippocampal regions are related to short-term motor skill learning. To investigate this, we utilized representational similarity analysis (RSA) of fMRI data collected while participants were learning four distinct motor sequences. Our analyses found substantial pattern separation in the cortical regions related to the motor task. Furthermore, the similarity between these cortical activity patterns and those in the hippocampus during interleaved rest periods accounted for individual learning performance. These finding suggest that the hippocampus preserves the representational patterns within the motor-related cortex during wakeful rest, which is potentially linked to rapid consolidation of motor memory, thereby enhancing overall learning performance.

Disclosures: S. Yoon: None. **S. Kim:** None.

Poster

PSTR112. Human Motor and Skill learning

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR112.26/TT28

Topic: H.10. Human Learning and Cognition

Support: NIH R01MH109520
NSF 2219323

Title: Rapid learning to automaticity reveals learned content stored within patterns of resting-state functional connectivity changes

Authors: *R. SANCHEZ-ROMERO[1], R. CHEN[1], N. LALTA[1], T. ITO[2], R. D. MILL[1], M. W. COLE[1];
[1]Rutgers Newark Ctr. for Mol. and Behavioral Neurosci., Newark, NJ; [2]T.J. Watson IBM Res. Ctr., Yorktown Heights, NY

Abstract: To study how rapidly learned automatic processes are supported by functional connectivity changes, we introduce a stimulus-response (SR mapping) learning paradigm able to evoke automatic processes in a short time (a single 32 min training session, Fig 1). This contrasts with typical cognitive psychology approaches of using 15 or more sessions to achieve automaticity. We use a dense repetition of 4 SR mappings to strongly engage co-activation of regions involved in the learning. To assess automaticity, we run a follow-up testing session, where 2 SR mappings are flipped to produce incongruent trials. We hypothesized that training would produce automaticity, as evidenced by lower response accuracy for incongruent trials, given the difficulty of counteracting learned automatic responses.
32 participants. Resting state fMRI from 2 pre and 2 post training runs. Functional connectivity (rsFC) inferred with ridge regression. Classification with a linear support vector machine.
To determine the effects of our paradigm on connectivity, we use rsFC changes (post - pre training) to classify between session A and B. We observed a sig. accuracy (70%, permutation

testing $p < 0.001$) suggesting that rsFC changes encode learning-related information. We observed rsFC changes in default mode, visual, frontoparietal and motor networks that are highly relevant for the classification. We didn't observe sig. accuracy when using only pre-rsFC (42% $p = 0.9$) or only post-rsFC (48% $p = 0.6$) suggesting rsFC changes effectively encode learning-induced effects.

To assess automaticity we compared response accuracy for incongruent and congruent trials. We confirmed a significant lower accuracy in incongruent trials (mean acc diff = -0.08, $p = 2.2e\text{-}13$), suggesting that participants were prone to incorrect answers given the difficulty of counteracting learned automatic mappings.

Together, these results provide evidence that connectivity-supported automatic processes can be produced in a short time via a paradigm that strongly engages the co-activation of distributed regions involved in rapid learning.

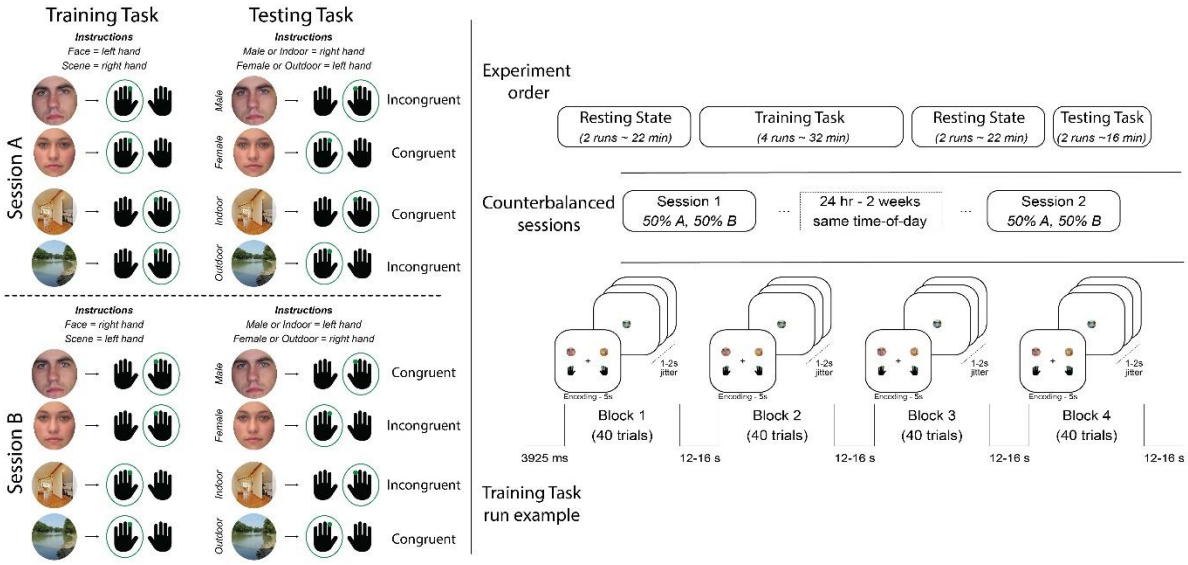

Figure 1. Rapid learning paradigm schematic. Left panel: Two different visual stimulus - motor response (SR) mappings (A and B) for the Training and Testing sessions . **Right panel**: Experiment order under MRI (top); counterbalanced sessions across participants in different days (middle); training task run example (bottom).

Disclosures: R. Sanchez-Romero: None. **R. Chen:** None. **N. Lalta:** None. **T. Ito:** None. **R.D. Mill:** None. **M.W. Cole:** None.

Poster

PSTR112. Human Motor and Skill learning

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Topic: H.10. Human Learning and Cognition

Support: the National Research Foundation of Korea (NRF-2021R1A2C2011648)
Hanyang University (HY-202000000002753)

Center for Neuroscience Imaging Research, Institute for Basic Science, Korea (IBS-R015-D1)

Title: Whole-brain functional connectome predicts individual differences in learning a motor skill

Authors: *J. KIM[1], K. YOO[2], S. KIM[1,3];
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Abstract: Learning a motor skill (e.g., playing golf) in the real world often requires continuous attention on visual feedback providing a mapping between our actions and their consequences. Thus, it involves complicated interaction across the whole brain, which is not limited to sensorimotor regions, and the interaction pattern may determine the extent to which individuals learn a motor skill, thereby being a key to understand individual differences in behavior. To investigate the whole-brain interaction underlying skill acquisition, we applied connectome-based predictive modeling (CPM) to the fMRI data acquired while participants were learning a complicated motor skill. Specifically, participants learned to control their fingers to move an on-screen computer cursor under two alternating conditions of continuous and discrete cursor feedback. As expected, our findings showed that learning occurs mostly in the continuous feedback condition. CPM analysis revealed that whole-brain functional connectivity during the early stage of learning successfully predicts an individual's ability to learn a complex motor skill measured by improvement in individual task performance following learning (r=.512, permutation p=.025).

Disclosures: **J. Kim:** None. **K. Yoo:** None. **S. Kim:** None.

Poster

PSTR112. Human Motor and Skill learning

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Program #/Poster #: PSTR112.28/UU2

Topic: H.08. Learning and Memory

Support: ANR grant awarded within the framework of the Inserm CPJ
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National Brain Research Program (project 2017-1.2.1-NKP-2017-00002)
NKFI/OTKA K funding scheme 128016

Title: Neurophysiological insighs into probabilistic sequence learning: Unraveling the dynamics of neural representations and rewiring processes

Authors: *T. VÉKONY[1], A. TAKACS[2], F. PEDRAZA[3], F. HAESEBAERT[1], B. TILLMANN[4], C. BESTE[2], D. NEMETH[1];
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Psychiatry, TU Dresden, Dresden, Germany; [3]Lab. EMC, Univ. Lyon 2, Lyon, France; [4]Lab. d'Etude de l'Apprentissage et du Développement, Univ. de Bourgogne, Dijon, France

Abstract: Probabilistic sequence learning plays a crucial role in skill development and facilitates predictive processing. In order to investigate the neural processes underlying the learning and rewiring of probabilistic sequences, we conducted a study on healthy adults. We employed both univariate analyses and multivariate pattern analyses (MVPAs) to examine the temporally decomposed EEG signals acquired over a span of three days. This allowed us to observe the progression from initial sequence learning on Day 1 to the integration of new information and the modification of existing knowledge on Day 2, as well as the stability of both forms of knowledge on Day 3. The MVPAs revealed that all three codes of the decomposed EEG signals contribute to the neurophysiological representation of the learned probabilities. Furthermore, we observed that the neural representation of new knowledge becomes more stable after the rewiring process takes place. These findings emphasize the intricate nature of probabilistic sequence learning and provide insights into the dynamic interplay between different coding mechanisms. The involvement of both perceptual and motor coding in the learning of sequential regularities suggests a comprehensive integration of sensory and motor processes. Moreover, the increased stability of neural representations following the rewiring process suggests a refinement and consolidation of the newly acquired knowledge.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR113.01/UU3

Topic: H.11. Language

Title: Phase alignment of low-frequency neural activity to the amplitude envelope of speech reflects evoked responses to acoustic edges, not oscillatory entrainment

Authors: *Y. OGANIAN[1], K. KOJIMA[2], A. BRESKA[3], A. FINDLAY[4], C. CAI[4], E. F. CHANG[5], S. NAGARAJAN[6];
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Abstract: The amplitude envelope of speech is crucial for accurate comprehension. Considered a key stage in speech processing, the phase of neural activity in the theta-delta bands (1 - 10 Hz) tracks the phase of the speech amplitude envelope during listening. However, the mechanisms

underlying this envelope representation have been heavily debated. A dominant model posits that envelope tracking reflects
entrainment of endogenous low-frequency oscillations to the speech envelope. Alternatively, envelope tracking reflects a series of evoked responses to acoustic landmarks within the envelope. It has proven
challenging to distinguish these two mechanisms. To address this, we recorded magnetoencephalography while participants (n=12, 6 female) listened to natural speech, and compared the neural phase patterns to
the predictions of two computational models: An oscillatory entrainment model and a model of evoked responses to peaks in the rate of envelope change. Critically, we also presented speech at slowed rates, where the spectro-temporal predictions of the two models diverge. Our analyses revealed transient theta phase-locking in regular speech, as predicted by both models. However, for slow speech we found transient theta and delta phase-locking, a pattern that was fully compatible with the evoked response model but could not be explained by the oscillatory entrainment model. Furthermore, encoding of acoustic edge magnitudes was invariant to contextual speech rate, demonstrating speech rate normalization of acoustic edge representations. Taken together, our results suggest that neural phase
locking to the speech envelope is more likely to reflect discrete representation of transient information rather than oscillatory entrainment.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.02/UU4

Topic: H.11. Language

Support: the Brain Program of the IDEAS Research Center
Vernadski scholarship

Title: Brain-rhythm-based inference for time-scale invariant speech processing

Authors: *O. DOGONASHEVA[1,2], O. PLATONOVA[3], D. ZAKHAROV[2], A.-L. GIRAUD[3], B. GUTKIN[1];
[1]École Normale Supérieure de Paris, PARIS, France; [2]HSE Univ., Moscow, Russian Federation; [3]Inst. De L'audition, Pasteur Inst., Paris, France

Abstract: Speech processing, with its temporal cadence and multi-scale of syntactic invariants (syllables, words), is a paradigmatic example where rhythms have been proposed to play a key role [1], with a speech-modulated hierarchical structure of intercoupled cortical oscillations correlating with successful comprehension. Experiments show that speech recognition remains

largely intact when compressed up to a certain temporal factor [2] and the re-spacing of chunks of incomprehensible compressed speech with silences recovers comprehension. We hypothesize that rhythm-based top-down semantic context inference is a key mechanism for such re-spaced recovery of compressed speech. We propose a computational model that incorporates a wide range of brain-rhythm data mechanistically and accounts for time-invariant word recognition. In this model, the hierarchically arranged interacting rhythms actively maintain top-down and bottom-up information flow during the inference process: theta-gamma interactions predict and parse phonemes/syllable sequences, while the delta-rhythm adaptively generates the inferred context. We show that word recognition degrades when the speed of words and syllables is compressed beyond the delta and theta rhythms, respectively. The top-down contextual delta-implemented context allows us to explain why re-spacing compressed speech recovers comprehension. Brain-Rhythm-based Inference (BRyBI) model further predicts that delta-implemented context allows for syllable parsing without a precise locking of the theta-rhythmic activity.

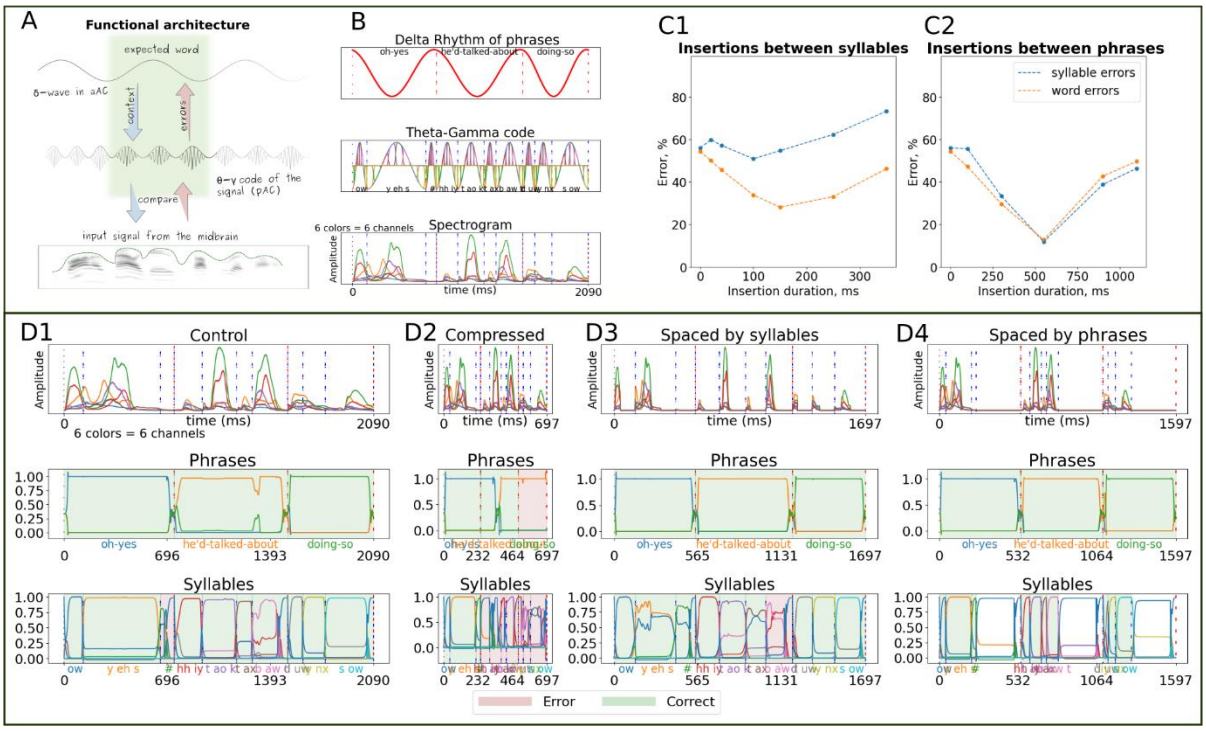

Fig. (A) BRyBI model. (B) An example of reconstructed rhythms. (C) Errors in recognition of preprocessed speech. (D) An example of speech recognition: spectrogram (top); phrase (middle) and syllable (bottom) probabilities. (D1) Speech without preprocessing; (D2) Compressed speech; (D3) compressed speech and 100 ms silence between syllables; and (D4) 300 ms silence between phrases.

[1] Giraud AL, Poeppel D. Nat Neurosci (2012).[2] Ghitza O, Greenberg S. Phonetica (2009).

Disclosures: **O. Dogonasheva:** None. **O. Platonova:** None. **D. Zakharov:** None. **A. Giraud:** None. **B. Gutkin:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR113.03/UU5

Topic: H.11. Language

Support: Samuel F. Hulbert Chair Endowment

Title: Single-trial identification of grammatical, syntactic, and semantic errors in rapid serial visual presentation using common spatial patterns and quadratic discriminant analysis

Authors: A. W. L. CHIU, *A. SHERMAN, M. WITT;
Biol. and Biomed. Engin., Rose-Hulman Inst. of Technol., Terre Haute, IN

Abstract: Brain-computer interface (BCI) spellers can serve to restore the means of communication for individuals with severe neuromuscular deficiencies. Previously, we have identified potentially important EEG amplitude, timing, and frequency features and developed machine-learning strategies to classify grammatical, syntactic, and semantic error identification errors in BCI spellers. An OpenBCI 16-channel EEG system with Cyton and Daisy board setup is used for data acquisition. Subjects are presented with 240 sentences (ranging from 6 to 15 words in length) using an optimal recognition point (ORP) paradigm in rapid serial visual presentation mode where each word was shown in rapid succession (60 words per minute) to simulate the use of a BCI speller in sentence construction. Each sentence has an equal probability of containing either a semantic error (SM), a syntactic error (SY), a grammatical error (G), or no error (Control). EEG features such as ERP (N400, P600 intensities, and latencies), as well as frequency band power (alpha and theta) are extracted within one second of the presentation of each word. Common spatial pattern (CSP) is used to recast the high-dimensional overlapping feature space of multiple classes to maximize the ratio of the variances along the two principal axes. We train four binary quadratic discriminant analysis (QDA) classifiers to distinguish each word into one of the four possible outcomes (SM, SY, G, and Control) in the newly projected 2D feature space using a five-fold cross-validation method. In each classifier, the hyperbolic boundary of each QDA would be created in such a way that its principal axis would be the projected dimension that corresponds to the largest variance in each projected error state after CSP. This way, the classifier would be less likely to provide false positive outputs, namely, it would be more likely to miss an error than to incorrectly identify a correct word as wrong. A model is created and evaluated for each subject (N=6), without any need for aggregated analysis. The offline single-trial evaluation shows some promising initial results with accuracies of (95±2% for Control; 49±4% for SM; 41±7% for SY; and 50±5% for G). Furthermore, the coefficients of the CSP projection matrix may provide valuable information on the relative importance of the original ERP-based and frequency-based features in each EEG location.

Disclosures: **A.W.L. Chiu:** None. **A. Sherman:** None. **M. Witt:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.04/UU6

Topic: H.11. Language

Support: NIH Grant NINDS 1R01NS109367
NIH Grant NINDS 1R01NS115929
NIH Grant NIDCD R01DC018805

Title: Investigating Network Similarity Changes During Language Perception and Production

Authors: *Y. ESMAEILI[1], A. KHALILIAN-GOURTANI[2], P. DUGAN[3], D. FRIEDMAN[4], W. K. DOYLE[2], O. DEVINSKY[2], A. FLINKER[2];
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Abstract: Functional connectivity (FC) is a prevalent technique in neuroimaging to elucidate brain networks and dynamics. A large body of literature focuses on intrinsic networks derived from resting-state data, however, how these networks change over short time periods and interact with cognitive states remains poorly understood. Our study leverages the excellent spatiotemporal resolution of electrocorticography (ECoG) to address this gap by investigating how neural FC is modulated focusing on network similarity during language tasks shifting from perception to production. We acquire recordings from five neurosurgical patients while they perform a battery of language production tasks (auditory naming, word repetition, sentence completion, picture naming, and visual reading). We extract high-gamma broadband neural activity (70-150 Hz), which is correlated with the BOLD response, and compute an average signal associated with each of the 17 network parcellations widely used in neuroimaging studies (Yeo et al. 2011). We compute the FC between each network signal and each electrode, which allows us to quantify the similarity between networks rather than electrodes (correlation between FC for each network and all the electrodes). When analyzing resting state ECoG data, we replicate the results of Yeo et al. When applying to our task data we either regress out the mean activity (replicating FC as shown by Cole et al. 2014) or leave it in (estimating cognitive task effects). Capitalizing on the temporal resolution of ECoG, we are able to examine these network similarities during stimulus presentation and speech production. We show an increase in the similarity matrices for somatomotor and default mode networks, representing relative increase of these FC networks when the stimulus effect is present (i.e. not regressed out). By measuring the difference of electrode-networks between regressed and non-regressed FC, we can find electrodes that significantly contribute to network similarity changes (p-value &lt 0.01). We find connectivity increases in sensory electrodes across tasks during stimulus presentation with the somatomotor and default B networks. As the tasks shift from perception to production we find increases in speech motor electrodes across tasks with the somatomotor and default A networks. Interestingly, we also find a decrease in connectivity across temporal cortex electrodes during speech production with the somatomotor network. In sum, we report an approach to network

analysis that replicates the resting-state literature but capitalizes on temporal resolution to elucidate major network changes during cognitive states in language tasks.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.05/UU7

Topic: H.11. Language

Title: Individual differences in hemispheric lateralization of language-related neural processing among elementary-aged children.

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Abstract: Developing language processing skills is a major task of early cognitive development, undergirded by a complex array of neural substrates. Typical mechanisms for language learning have become a more common topic of study given the growing body of neuroimaging tools. However, the extent to which individual differences influence these neural mechanisms or their implications for cognitive outcomes are often overlooked. We analyzed *magnetic resonance imaging (MRI)* data from age-7 children (*N*=159) as they judged whether auditory sentences with varied semantic (*task S*) or grammatical (*task G*) errors were correct. We quantified mean left and right hemisphere *blood oxygen-level dependent (BOLD)* signal in first-level contrasts of sentence task > perceptual/motor control. We estimated multilevel models with random intercepts predicting BOLD signal in either hemisphere based on task demands (i.e., semantic or grammatical). *Intraclass correlation coefficients (ICCs)* quantified the added value of accounting for the nesting of task-level values within subjects (i.e., individual differences). To examine the behavioral implications of lateralization patterns, we estimated models predicting accuracy (i.e., percent trials correct) based on task demands or hemispheric BOLD signal. We found significantly higher right hemisphere activity for task G compared to task S *(B= 0.08, SE= 0.02, p<.001*). ICCs for the right (0.34) and left hemisphere (0.41) models suggest that 34% and 41% of variability in activity was explained by subject-level trends. Left hemisphere activity was negatively related with accuracy (*B=-21.78, SE=9.91, p=.029*) and performance was significantly lower for task G versus task S (*B=-7.79, SE= 2.63, p=.003).* Language processing is shown to be mostly left lateralized, an effect which increases as a function of content mastery. Children often develop skills with language semantics prior to syntax or grammar. Our findings somewhat support these models: children in this study showed both lower accuracy and greater

right hemisphere activity during the ostensibly more difficult task G. However, the negative association of left hemisphere activity with accuracy aligns more with other models that describe negative associations between overall neural activity and language expertise. These results show that same-age children can rely on markedly different neurocognitive mechanisms to process the same content. This illustrates the added value of accounting for individual differences in studies of neurodevelopment, and demonstrates an application for multilevel modelling approaches in future neuroscience studies.

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Poster

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Topic: H.11. Language

Support: P50 DC014664

Title: A resting-state fMRI study of network hypo- and hyper- connectivity differences predicting post-stroke aphasisa: location and distance matter

Authors: *H. ZHU[1], M. C. FITZHUGH[2], L. KEATOR[3], L. JOHNSON[4], C. RORDEN[4], L. BONILHA[5], J. FRIDRIKSSON[4], C. ROGALSKY[1];
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Abstract: Recent research indicates that resting-state functional MRI connectivity of the dual-stream cortical speech network can serve as a potential predictor of language impairments in individuals who have experienced a stroke. However, it remains unclear how hyper- versus hypo-functional connectivity contributes to impairment, and how local versus more distant network changes also may be contributing to impairments. To address these questions, we examined resting-state fMRIs of 28 chronic left-hemisphere stroke survivors with aphasia and 28 neurotypical matched controls. Language performance was evaluated using the Western Aphasia Battery. SPM12 and in-house MATLAB scripts were used for fMRI preprocessing and functional connectivity calculations. Statistical analyses, including independent sample t-tests and linear regression were calculated. Results include: 1) compared to the control group, the aphasia group exhibited significant hyper-connectivity both between hemispheres and within the left hemisphere, but no differences in right intra-hemisphere functional connectivity; 2) hypo-functional connectivity was found to be both a significant positive predictor of some specific language abilities (i.e., auditory verbal comprehension) and a negative predictor of others (repetition, naming, and aphasia severity), depending on the specific stream of the speech network examined; we found no evidence of hyper-functional connectivity predicting language

performance in either direction; 3) differences in functional connectivity between the aphasia and control groups was significantly positively correlated with ROI distance. Overall, our results suggest the importance of hypo-functional connectivity in predicting language performance, in particular long-range functional connectivity which appears to be most vulnerable in post-stroke aphasia. We conclude that strokes leading to aphasia tend to compromise long-range connectivity, and that shorter-range connectivity differences may reflect a compensatory response.

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Poster

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Topic: H.11. Language

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Title: Low frequency and high gamma oscillations differently tracked hierarchical linguistic structures in speech: evidence from intracranial EEG recordings

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Abstract: In speech communication, the human brain can rapidly construct linguistic structures at various hierarchies (such as syllables, words, phrases and sentences) to comprehend speech (Ding et al., 2016). Previous research has demonstrated the significance of low frequency oscillations (e.g. delta and theta bands) in parsing linguistic units. However, it remains elusive how high-gamma oscillations relate to the construction of linguistic structures during speech perception. In the present study, we used intracranial stereo-electroencephalography (sEEG) to record neural activities from 20 subjects while they were listening to continuous speech stimuli that contained syllables, phrases or sentences. We employed a frequency-tagging paradigm to tag neural activities at different linguistic rates of 1 Hz, 2 Hz and 4 Hz. We analyzed Inter-trial phase coherence of low-frequency signals collected from intracranial electrode contacts throughout the whole brain. The results indicated that the low-frequency oscillations in the temporal and frontal language network tracked higher-level structures (i.e. phrases and sentences), and those in the bilateral primary auditory cortex clearly encoded low-level tracking to syllables at 4 Hz. Furthermore, high-gamma activities tracked syllabic rate at 4 Hz, but the tracking activity was much weaker at the higher-level linguistic rates. The results suggest that low frequency and high-

gamma oscillations differently tracked hierarchical linguistic structures in speech. This study will advance our understanding of how neural oscillations underpin linguistic processing and listening comprehension during speech communication.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Topic: H.11. Language

Support: TUM Innovation Network Neurotechnology in Mental Health

Title: Cellular and circuit mechanisms of right-hemispheric language functions in aphasia

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Abstract: Damage to the left-hemispheric brain regions of the human language system can lead to detrimental long-term deficits in language production and comprehension. A large body of evidence has shown that language functions are amenable to neurological rehabilitation. This recovery of linguistic abilities is hypothesised to be driven by a reorganisation of the language network whereby preserved cortical structures in perilesional and right-hemispheric homotopic areas compensate for the loss of brain tissue. The neuronal mechanisms underlying such reorganisation are not well understood. To obtain insights into the role of the right hemisphere in language recovery at the single-neuron and neuronal circuit level, we chronically implanted a patient with aphasia with four intracortical planar microelectrode arrays (256 channel total). Specifically, we targeted right-hemispheric homotopic areas of the language network and placed arrays in the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supramarginal gyrus (SMG) and angular gyrus (AG). These extracellular recordings allowed us to monitor large-scale neuronal activity with millisecond and sub-millimeter resolution and capture single unit spiking activity as well as local field potentials. Neuronal data acquisition proceeded in parallel to the patient performing a variety of language-related tasks. Experimental sessions were conducted multiple times per week over the course of several months and covered three central pillars of language, namely single word comprehension, word production and word repetition. The tasks were designed to allow us to contrast language-related neuronal responses associated with processing of stimuli of different linguistic complexity, of different semantic, syntactic and phonological categories, and under different task demands. Our preliminary findings argue for a role of the right hemisphere in language functions. Specifically, we observed locking of single

unit responses to different trial events that was task-specific (word repetition vs. retrieval) and brain region-specific (prefrontal vs. parietal cortex). For example, we recorded changes in IFG and MFG unit activity prior to speech in both repetition and naming tasks, suggesting a role of these regions in speech planning and word retrieval. In contrast, SMG responses were more prominent after speech onset, in agreement with a role in vocalisation. An in-depth understanding of the mechanisms underlying functional reorganisation and neuronal plasticity in the human brain will promote novel therapeutic approaches for individuals with disorders of language and other higher cognitive functions.

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Poster

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Topic: H.11. Language

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Title: End-to-end automatic speech recognition explains the hierarchical encoding of language in the auditory pathway

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Abstract: Linguistic information of speech is represented hierarchically in the auditory pathway, such that higher-order representations emerge as we get further away from the primary auditory cortex. But how or why these different levels of representations emerge in the brain remains a matter of debate. An unbiased (data-driven) computational model of speech processing can be used to answer this question. Developing data-driven computational models directly using neural data is next to impossible, given the scarcity of neural data compared to synthetic data modalities (text, image, audio, etc.). A common approach to overcome this limitation is to train a deep neural network on a large corpus to perform a human-relevant task and learn insights about the brain processes by comparing the representations of the artificial model and biological neural populations. For example, there is increasing interest in using large language models trained to predict the next word in a sequence to predict brain activity when listening to speech. A crucial difference between these models and the speech processing neural pathway is that the input to the auditory system is a highly variable sound which such models ignore when using the transcript. In this work, we address the question: If we train a data-driven model to perform the task of speech recognition from start to finish (spectrogram to word sequence), can it: (1)

Explain the extraction of linguistic information observed in the brain? (2) Reveal the anatomical organization of speech processing steps? We use an RNN-Transducer as a computational model of speech perception. Our model consists of 6 LSTM layers that process sound and one feedback LSTM layer that uses the model's previous predictions to influence its next decision. We map the model layer activations to intracranial (ECoG & sEEG) activity recorded from human neurosurgical patients and label each electrode by its best predictive layer of the model. We observe that deeper layers of the model better predict the downstream areas in the auditory pathway, shedding light on the anatomy of stages of speech processing. To identify the cause of this improved prediction accuracy, we determine the degree of linguistic feature encoding in RNN-T layers, from subphonetic to semantic. This analysis reveals the emergence of a hierarchy of language representation in the model such that earlier layers are best at predicting phoneme-level information and later ones at word-level information. Together, these two levels of analysis show a progressive encoding of linguistic information across different layers of the network and how these computations map to different regions of the auditory cortex.

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Poster

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Title: Investigating spatiotemporal features of semantic processing: intracranial neural decoding during speech production

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Abstract: The act of language processing involves three fundamental elements: semantics, auditory, and articulation. Semantic processing, which captures both linguistic meaning and speaker intentions, is believed to occur at the initial stage of speech comprehension. However, despite the importance of semantics in speech, a significant gap exists in speech BCI research regarding the specific neural mechanisms underlying this process. In the present study, we aim to decode semantics from human intracranial recordings during speech production tasks and investigate spatiotemporal features in language processing.
Seven epilepsy patients had surgical implantation of electrocorticography in clinically relevant

cerebral regions for monitoring. Recordings were obtained during a word reading task using intracranial electrodes. The spoken words were categorized into semantic groups, specifically distinguishing between body parts and non-body parts, or between agents and actions. Bandpass filtering and Hilbert transform were applied to extract amplitudes corresponding to specific frequency bands from the brain signals. Using a decision tree algorithm, the classification of semantic categories based on neural features involved decoding for each time window interval of 100ms.
The best performing subject had an accuracy of 75.9 ± 1.95 percent in both semantic categories. In the temporal dimension, the time window from 400ms to 500ms after word onset showed the most promise for successful semantic decoding. The importance of spatial features included left superior temporal gyrus (STG), medial temporal gyrus (MTG), and dorsolateral prefrontal cortex.
Our findings have elucidated the key components engaged in initial language processing via successful decoding. Specifically, the result on temporal features aligns with prior research indicating the involvement of N400 in semantic processing. Furthermore, the results on spatial aspects encompass critical regions highlighted from the previous studies related to speech decoding, namely STG and MTG. A practical implementation of semantic decoding involves integrating it with auditory and articulatory techniques to enhance the effectiveness of the current speech BCI technique.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.11/UU13

Topic: H.11. Language

Title: Source-resolved event-related potentials reveal differences in hemispheric recruitment for joke comprehension between left- and right-handers

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Abstract: Most people exhibit language lateralization to the left hemisphere although left-handers are less lateralized than right-handers. However, few studies have addressed the association between handedness and hemispheric asymmetry in high-level language processing such as joke comprehension. This study combines regression with the source-resolved event-related potential (ERP) technique to examine whether the amplitude of single-trial cortical ERPs elicited by the critical words in jokes and non-funny controls can be explained by condition, handedness, and/or statistical characteristics of the words. Electroencephalogram data were

recorded from 17 left- and 17 right-handers as they read one-line jokes and non-funny control stimuli. The activities and locations of cortical sources were estimated by applying independent component analysis to the scalp recordings. The source activities from all the participants were mixed and then clustered based on their estimated locations. The amplitude of single-trial ERPs of each cluster was then measured by averaging across the time window of a language-related ERP component (500 - 900 ms). The predictability of the critical words in the joke and non-funny stimuli was measured using cloze probability (from a survey of human subjects) and surprisal derived from the large language model GPT3. A series of linear mixed-effects models, which included handedness, experimental condition (i.e., joke or control), and predictability measures as fixed effects and subject as a random intercept term, were constructed to predict the amplitude of the single-trial ERPs. Single-factor regressions revealed that the amplitude in the right prefrontal and middle frontal areas was significantly predicted by the cloze probability (right prefrontal: $p = 0.001$; middle frontal: $p = 0.001$) and surprisal (right prefrontal: $p < 0.001$; middle frontal: $p = 0.004$), whereas the amplitude in the left prefrontal, temporal, and parietal areas was not. Furthermore, two-way interactions between handedness and condition revealed that relative to left-handers' responses to jokes, right-handers showed significantly greater amplitude in the left prefrontal ($p = 0.023$) and left parietal areas ($p = 0.015$), and reduced amplitude in left temporal ($p = 0.049$) and right parietal areas ($p = 0.011$). The results suggest that the anterior sources were more sensitive to the contextual probability of words than the posterior sources. In addition, the left and right parietal sources showed significant interaction effects between handedness and condition, suggesting increased recruitment of the right hemisphere in left-handers.

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Poster

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Topic: H.11. Language

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Title: White Matter Tracts in Language Processing: Insights from Structural Disconnection Mapping

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Abstract: **Introduction:** The Western Aphasia Battery (WAB) is an integral tool in aphasia assessment. It can be used to assess the severity of language impairment following stroke, as indexed by the aphasia quotient (AQ) and other subtests. Lesion-symptom mapping (LSM) studies have indicated roles for particular cortical areas, such as inferior frontal, superior and middle temporal, and inferior parietal cortices in WAB performance (Bates et al., 2003; Baldo et al., 2006). Furthermore, white matter tracts like the Arcuate Fasciculus (AF) (Catani et al., 2005; Ivanova et al., 2021), Superior Longitudinal Fasciculus (SLF) (Makris et al., 2005), Uncinate Fasciculus (UF) (Papagno, 2011), Inferior Longitudinal Fasciculus (ILF) (Catani et al., 2003), Inferior Fronto-Occipital Fasciculus (IFOF) (Catani et al., 2002), and Frontal Aslant Tract (FAT) (Catani et al., 2012; Zhong et al., 2022) play significant roles in language comprehension and production. Despite these findings, our grasp on white matter tracts remains less comprehensive than cortical areas. **Methods:** White matter correlates of behavioral scores on the WAB were assessed in 130 left-hemisphere stroke survivors using indirect structural disconnection mapping via the lesion quantification toolkit (Griffis et al., 2021) to determine how the severity of white matter tract-level disconnection is correlated with different WAB subtests (Bonferroni-corrected alpha = 0.005). **Results & Discussion:** Correlation analyses showed that the disconnection of the inferior longitudinal fasciculus (ILF) and the posterior segment of the corpus callosum (CCPoeror) affected the performance of all WAB subtests.The ILF connects the occipital and temporal lobes, which may integrate visual information with language processes, aiding in language production and comprehension. The CCPoeror was also shown across subtests and may enable the transfer of information between the language-related regions of the left and right cerebral hemispheres. The uncinate fasciculus (UF) was found in the correlation analysis to affect performance of most WAB subtests. The UF contains short connections between the anterior temporal lobe and the inferior frontal lobe, which may support domain general aspects of language as it was found across all subtests, except for a comprehension subtest and writing, in which success may rely more on core components of the language system. In conclusion, this study underscores the integral role of white matter tracts, specifically, the ILF, CCPoeror, and UF in language-related processes as they significantly correlate with performance on the WAB subtests.

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Poster

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Topic: H.11. Language

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Title: Causal mechanisms underlying self-agency

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Abstract: Self-agency is the experience of being the agent of one's own thoughts and actions. The experience of self-agency is thought to result from a minimal prediction error between the predicted sensory consequence of a self-generated action and the actual outcome. This self-prediction ability is critical for speech monitoring where we continually compare auditory feedback (i.e., what we hear ourselves say) with what we expect to hear. When subjects hear such minimal perturbations in their auditory feedback while speaking, they typically make compensatory corrective responses that oppose the direction of perturbation, indicating that they judge the perturbations as errors in their speech output. However, it is unclear as to whether these corrective responses are modulated by subjects' reliance on internal predictions about the outcomes of their actions based on their prior experience of sensorimotor feedback. If increased reliance on self-predictions results in the experience of self-agency, we would expect that subjects who rely more on their self-predictions to guide their speech output, will consequently rely less on external auditory feedback, resulting in smaller corrective responses and an enhanced sense of self-agency that they followed their internal predictions to generate their own actions (i.e., their speech output). We have found that the medial prefrontal cortex (mPFC) is a potential neural substrate of this self-prediction ability. Here, we examine whether increasing mPFC activity with high-frequency 10Hz repetitive transcranial magnetic stimulation (rTMS) will enhance subjects' reliance on their self-predictions during speech monitoring so that they make smaller corrective responses to perturbations in their auditory feedback to predict better self-agency judgments. Preliminary results reveal that after rTMS targeting mPFC, healthy control subjects (HC) showed significant increases in mPFC activation (N=15), which drove a significant reduction in compensatory corrective responses and improved self-agency judgments, compared to HC in the control rTMS condition (N=15). Together, these findings suggest a causal role of mPFC function in the experience of self-agency that results from the ability to make reliable predictions about the outcomes of self-generated actions.

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Poster

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Title: Fast & Accurate Classification of Task Structures in ECoG Generalizes to Continues Recordings

Authors: *A. KHALILIAN-GOURTANI[1], Y. ESMAEILI[2], P. DUGAN[3], D. FRIEDMAN[4], W. K. DOYLE[1], O. DEVINSKY[1], A. FLINKER[1];
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Abstract: *Introduction:* Human neuroscience has shifted towards unstructured, naturalistic stimuli combined with continuous neural recordings for deeper insights into brain dynamics. While this transition from structured task-based data allows for a more comprehensive understanding of neural activity, it comes at the cost of increased complexity and the need for laborious manual annotations, especially for motor tasks. We ask if learning from different stages of task-based structures can help us identify relevant events in continuous neural recordings? *Method:* We use electrocorticography (ECoG) recordings from five neurosurgical patients with electrodes sampling presylvian and occipital regions while they perform speech production tasks varying in modality (auditory repetition, picture naming, and word reading). We extract neural activity (high gamma broadband: 70-150 Hz) during three event-related stages of each task (rest, stimulus presentation, and speech production; five class labels in total). For each subject, we train a classifier to predict the stage given the neural recordings. We extend the mini-ROCKET transform (mRT) to handle multivariate neural signals with unequal temporal lengths for feature extraction, followed by feature normalization and a logistic regression classifier. We compare mRT against two state-of-the-art methods: HIVE-COTEv2 (HC) and Catch22 with random interval sampling (CRI), using 4-fold stratified cross-validation. *Results:* First, we evaluate event-related classification performance on a hold-out set (a: accuracy, f: F1-score, t: training time in minutes). The mRT model achieves higher accuracy with faster training time (a: 94% f: 91% t: 2.1) compared with HC (a: 91% f: 86% t: 17.7) and CRI (a: 76% f: 72% t: 4.8). To test model generalizability to future recordings, a patient repeated the tasks in two sessions. The mRT classifier trained on one session (a: 93% f: 91%) generalizes well when tested on the other (a: 89% f: 83%), compared to low generalizability of HC (a: 83% f: 71%) and CRI (a: 66% f: 53%) . Applying trained classifiers to an unstructured stream of continuous neural recordings, show mRT can pinpoint the event windows with high accuracy (vs. annotated event onsets) while HC and CRI fail to find the transitions between some events. *Conclusion:* We evaluate classifiers trained on task-structured data for event detection in continuous neural activity streams. We report a fast and accurate classifier that generalizes well to continuous recordings. When scaled up, our model enables annotation and investigation of complex neural activity dynamics in naturalistic scenarios.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR113.15/UU17

Topic: H.11. Language

Support: Neuroscience Innovation Foundation

Title: Role of the pre-supplementary motor area in syntax: a transcranial alternating current stimulation (TACS) study

Authors: C. LEUNG, ***M. HEARD**, K. E. MCLAREN, K. WOOD, Y. S. LEE;
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Abstract: Although the pre-supplementary motor area (pre-SMA) is often implicated as a part of speech and language processing networks, the functional role of the pre-SMA in syntax is not fully understood. Here, we targeted the pre-SMA using transcranial alternating current stimulation (TACS) of 18 Hz — a frequency elicited by sentence processing — during auditory sentence comprehension involving complex syntactic operations. Forty participants were pseudo-randomly assigned to TACS or sham group based upon their behavioral measures prior to the stimulation including non-verbal intelligence, verbal working memory, attention, and semantic knowledge (word spelling and definitions). These scores were matched between the two groups. During TACS, participants identified the grammatical agent of 100 object- (OR) and 100 subject-relative (SR) sentences. One participant was removed from analysis because they scored below chance. Both the active (20 participants) and sham groups (19 participants) were blind to the type of stimulation received, [$\chi^2 = 5.79 \times 10^{-31}$, $p = 1$]. The effect of TACS was first investigated with a general linear model with terms of stimulation type, syntax, language ability, auditory attention, and non-verbal intelligence. An interaction between stimulation type and syntax was included. There was a small, but significant main effect of stimulation group (active group accuracy = 94.7%, *SD* = 5.0%; sham group accuracy = 93.8%, *SD* = 4.8%; $z = 2.1$, $p = 0.035$). However, the interaction between group and syntax was not significant ($z = 1.6$, $p = 0.108$). As a *post hoc* follow-up, another model was constructed based on only OR sentences, as participants performed at ceiling on SR sentences (active group SR accuracy = 96.1%, *SD* = 3.6%; sham group SR accuracy = 95.7%, *SD* = 4.7%). We indeed found that TACS enhanced performance on OR sentences (active group OR accuracy = 93.4%, *SD* = 7.3%; sham group OR accuracy = 92.0%, *SD* = 6.3%; $z = 2.4$, $p = 0.016$). This is the first study showing a causal role of the pre-SMA and beta oscillations in syntax, which has implications for influential theories of rule-based temporal processing. Follow-up studies are under way to corroborate the initial findings.

Disclosures: C. Leung: None. **M. Heard:** None. **K.E. McLaren:** None. **K. Wood:** None. **Y.S. Lee:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.16/UU18

Topic: H.11. Language

Support: NIMH MH094258
Kiwanis Neuroscience Research Foundation

Title: Neuroanatomical correlates of item response patterns in the Controlled Oral Word Association Test

Authors: *C. DEIFELT STREESE[1], J. E. BRUSS[2], J. D. SKYE[2], J. MICHAELSON[3], D. TRANEL[4];
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Abstract: The Controlled Oral Word Association Test (COWAT), a longstanding measure of phonemic verbal fluency, is traditionally scored by counting the number of valid responses. However, this approach does not capture the richness and complexity of responses generated by individuals in the COWAT. Additional metrics, such as response frequency, complexity, or part-of-speech can help elucidate other important features of COWAT performance. As a proof of concept, we harnessed a large set of COWAT responses from a sample of 226 neurological patients with focal brain lesions and used lesion-to-symptom mapping (LSM) of noun-verb response ratios to identify neural correlates of noun and verb generation. Individual word responses to the COWAT were aggregated, and homonyms and homographs were excluded from the dataset. Noun and verb items were retained for analysis, and a noun-verb ratio was calculated for each individual, whereby values closer to 1 indicate the participant generated more verbs than nouns, and values closer to 0 indicate more nouns than verbs. Lesion masks and noun-verb ratios were used for LSM, using the LESYMAP package in R. As expected, results for both noun and verb generation were left-lateralized. A smaller proportion of verbs generated was associated with damage to regions in the precentral gyrus, whereas a smaller proportion of nouns generated was associated with damage to white matter structures within the temporal and frontal lobes. Our results replicated previous research, demonstrating a partial dissociation between the neural systems specialized for verb and noun retrieval. Like previous work, our results indicate that verb generation broadly localizes to the prefrontal gyrus. Whereas previous work localized noun generation more specifically throughout the temporal lobe, our findings suggest that a relative lack of noun generation in favor of verb generation is associated with damage to underlying white matter structures more broadly, which may reflect a more distributed nature of noun storage throughout the cortex. Here, we present data supporting the notion that item-level responses in COWAT performance by individuals with focal brain lesions are sufficiently sensitive to group patterns of word generation for use in LSM and can be used to query neural correlates of these processes. These findings give confidence that item analyses of words generated in the COWAT by participants with focal brain damage can yield further insights into the underlying neuroanatomical correlates of word generation.

Disclosures: C. Deifelt Streese: None. **J.E. Bruss:** None. **J.D. Skye:** None. **J. Michaelson:** None. **D. Tranel:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR113.17/UU19

Topic: H.11. Language

Support: Howard Hughes Medical Institute

Title: Human intraoperative Neuropixels recordings: experience and safety in a 56 patient case series

Authors: *J. E. CHUNG[1], J. P. ANDREWS[1], D. XU[1], Q. GREICIUS[1], M. K. LEONARD[1], L. GWILLIAMS[1], K. K. SELLERS[1], M. WELKENHUYSEN[2], B. DUTTA[2], C. R. CADWELL[1], E. F. CHANG[1];
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Abstract: The Neuropixels probe has made extracellular recording of large numbers of single neurons accessible across many animal models. Translation of these methodologies to human intraoperative recording has only recently been possible, and field-wide experience is from tens of patients distributed among only a few clinical sites and surgeons. Here, we report safety, histology, and electrophysiologic quality characterization from our single-surgeon case series of all 56 patients who have participated in Neuropixels intraoperative recording at our institution - the largest series to our knowledge. Participants ranged in ages from 18 to 74 with a variety of pathologies, all requiring resection of the tissue that the Neuropixels probe was inserted into. Importantly, 50/56 participants were awake during recording thereby demonstrating the safety and feasibility of the methodology to measure activity during task performance. We show that the methodology can be safe with no probe fractures in the most recent 50 cases. We compare histologic damage from Neuropixels recording sites to commercially available clinical devices. Intraoperative Neuropixels recording is a safe means to access single-neurons at a large scale in awake humans.

Disclosures: **J.E. Chung:** None. **J.P. Andrews:** None. **D. Xu:** None. **Q. Greicius:** None. **M.K. Leonard:** None. **L. Gwilliams:** None. **K.K. Sellers:** None. **M. Welkenhuysen:** A. Employment/Salary (full or part-time):; IMEC. **B. Dutta:** A. Employment/Salary (full or part-time):; IMEC. **C.R. Cadwell:** None. **E.F. Chang:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.18/UU20

Topic: H.11. Language

Support: NSF Grant BCS-1756313

Title: Investigating lexical representations for written and spoken words by re-analyzing an open dataset

Authors: *S. BANERJEE[1], S. R. DAMERA[2,3], V. PENDRI[3], M. RIESENHUBER[3]; [1]Neurosci., Georgetown Univ., Washington, DC; [2]Pediatrics, Children's Natl. Hosp., Washington, DC; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: How does the brain recognize words? Prior studies have established a 'lexicon' for written words in the ventral visual stream, known as the visual word form area (VWFA), which develops with experience and stores orthographic representations (Cohen et al., 2000; Glezer et al., 2009, Glezer et al., 2015, Lochy et al., 2018). Support for a lexical, rather than prelexical function (that is, storing representations of whole words instead of letter strings) of the VWFA was demonstrated via the frequency effect, wherein the VWFA shows decreasing activation in response to frequent words (Kronbichler et al., 2004). The frequency effect has been used as a tool to investigate lexical representations (Graves et al., 2010, Fischer-Baum et al.,2017). While the VWFA has been well studied, the location of lexical representations for spoken words are less well understood. The auditory lexicon was traditionally thought to lie in posterior superior temporal gyrus (STG), but a notable meta-analysis provided evidence for word-selective auditory representations in anterior STG (Dewitt & Rauschecker 2012), in the so-called "auditory word form area" (AWFA). Our group recently used fMRI-RA to provide evidence for an auditory lexicon in the AWFA (located at MNI: −62, −14, 2 (Damera et al. 2022, 2023).In the present study, we re-analyzed an open dataset (Mother-Of-all Unification Studies dataset) to further investigate the question of lexica in the brain using the word frequency effect during visual and auditory speech processing (Schoffelen et al 2019). Word frequencies were derived from the SUBTLEX-NL Dutch language database and the onsets of spoken words were tabulated using the Montreal Forced Aligner (Keuleers et al., 2010; Schillingmann et al., 2018). During reading, the VWFA shows the strongest negative effect of word frequency on activation, demonstrating that the frequency effect can localize lexica in the brain. In the speech listening condition, the frequency effect was strongest in the AWFA (MNI: -58, -6, -6, $p < 1e-09$), followed by several known hubs of the ventral auditory stream (Rauschecker & Scott 2009, Hickok & Poeppel 2004). By showing that the AWFA exhibits the frequency effect, we provide further support for the hypothesis that the aSTG contains an auditory lexicon.

Disclosures: S. Banerjee: None. **S.R. Damera:** None. **V. Pendri:** None. **M. Riesenhuber:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Topic: H.11. Language

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Title: Deactivation of the left inferior frontal gyrus at dual-step linguistic structuring: an fMRI study

Authors: *R. KASEDO[1,2], A. IIJIMA[1,2,3], K. NAKAHARA[4], Y. ADACHI[2], F. HOMAE[5], R.-I. HASHIMOTO[5], M. FUKUDA[6], H. SHIROZU[6], I. HASEGAWA[2];
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Abstract: Comprehension of written language requires dual-step structuring processes in which linear sequences of sublexical units are initially combined into lexical units, which are further composed into a sentence. Previous studies using functional magnetic resonance imaging (fMRI) and intracranial electrophysiological recording have shown build-up activity in the opercular part of the left inferior frontal gyrus (IFGoper) and triangular part of the left IFG (IFGtri) covarying with the number of lexical units to be structured. However, the neural underpinning of cross-hierarchical linguistic structuring remains unclear, presumably because the sublexical letterstring tracking in experienced readers proceeds too fast to be addressed with conventional neuroimaging approaches. To address this issue, we conduct fMRI in 42 participants by introducing a self-paced sequential letterstring reading task in which the participants read sentences, one letter after another, at their own pace. Since the reaction time (RT) to each letter was measured, the timing of the sublexical and lexical structuring could be estimated individually from the RT. To search for brain regions whose activity changes independently/dependently on the number of structured linguistic units at linguistic structuring, we performed general linear model (GLM) regression analyses and parametric analyses implemented in the Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/). The RT to the letters structuring linguistic units was significantly higher than that to the letters not structuring linguistic units. Moreover, the RT to the letters structuring lexical units increased with the number of structured lexical units. Thus, the participants' reading rhythm slowed down at the moment of linguistic structuring. Furthermore, activity in the left IFGoper transiently decreased independent of structured sublexical units when the participants structured sublexical units. By contrast, activity in the left IFGtri decreased with the number of structured lexical units, even when the build-up effects covarying with the number of accumulated lexical units were taken into account in the parametric GLM analyses. These results suggest that deactivation of the left IFG plays a key role in the dual-step structuring processes.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Topic: H.11. Language

Support: NSF Grant #1839379
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Title: Predictive processing in perception of artificial and natural signing avatar movement in signed language words leads to a cubic model of mu frequency power changes: An EEG study of signed language movement and familiarity

Authors: *A. S. WILLIS[1], L. C. QUANDT[2];
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Abstract: Recent research shows that deaf signers show increased behavioral and neural sensitivity to certain types of movement, such as biological motion, human actions, and signing avatars. However, other work suggests that in deaf signers exposed to signed language before age five, there is minimal involvement of the mirror mechanism during the perception of signed languages. The mirror mechanism is a neural mechanism where prior embodied experience is utilized for the perception of human movement. The disparity in those findings is a crucial question because of the emergence of signing avatars in educational technologies that are designed to engage learners' prior embodied experience for learning. To understand the role of the mirror mechanism in the perception of signing avatars' movements, we created stimuli that vary in four ways. Four signers differ in their movement and form, with two American Sign Language (ASL) Avatars producing either Motion Capture (Mocap) or Computer Synthesized (CS) signing movements and two real Humans signing either ASL or German Sign Language (DGS). Before and after the EEG experiment, deaf signers (N = 24) watched a brief signed phrase from each signer and provided with behavioral ratings. They were provided with a distractor task where they watched the movements of individual signed words for a sudden mid-movement freeze-frame, which were not included in analysis. We collected EEG oscillations, theta, alpha, mu, and beta frequency bands as they watched signed words. We conducted pre-planned and pre-registered ANOVA planned contrasts and time frequency analysis between each Signer Type. Compared to the pre-EEG experiment, we found a significant increase in self-reported behavioral rating of Familiarity with the Mocap Avatar after the EEG experiment ($p < 0.009$). While participants were observing a still Mocap Avatar before the onset of the signing movement, we found a significant synchronization in mu frequency compared to the other three

signers (min 3 electrodes, $p < 0.002$). During the perception of signers' movement, we found a pattern of significant power changes in mu frequency across signers that suggests a cubic model of sensorimotor processing. The observed cubic model suggests that deaf signers are highly familiar and efficient with simulation of real Human movement in signed language perception. The results also suggest that the Mocap Avatar is more familiar than the CS Avatar due to the embodied aspect of their movement. Our pre-registered EEG study suggests that during the perception of signed words, deaf signers engage their mirror mechanism for predictive processing and action simulation of human movements in signed words.

Disclosures: **A.S. Willis:** None. **L.C. Quandt:** None.

Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Title: Alpha and beta oscillations differentially support linguistic demands in a rule-switching task

Authors: *I. ZIOGA[1], Y. J. ZHOU[2], H. WEISSBART[1], A. G. LEWIS[3], A. E. MARTIN[4], S. HAEGENS[5];
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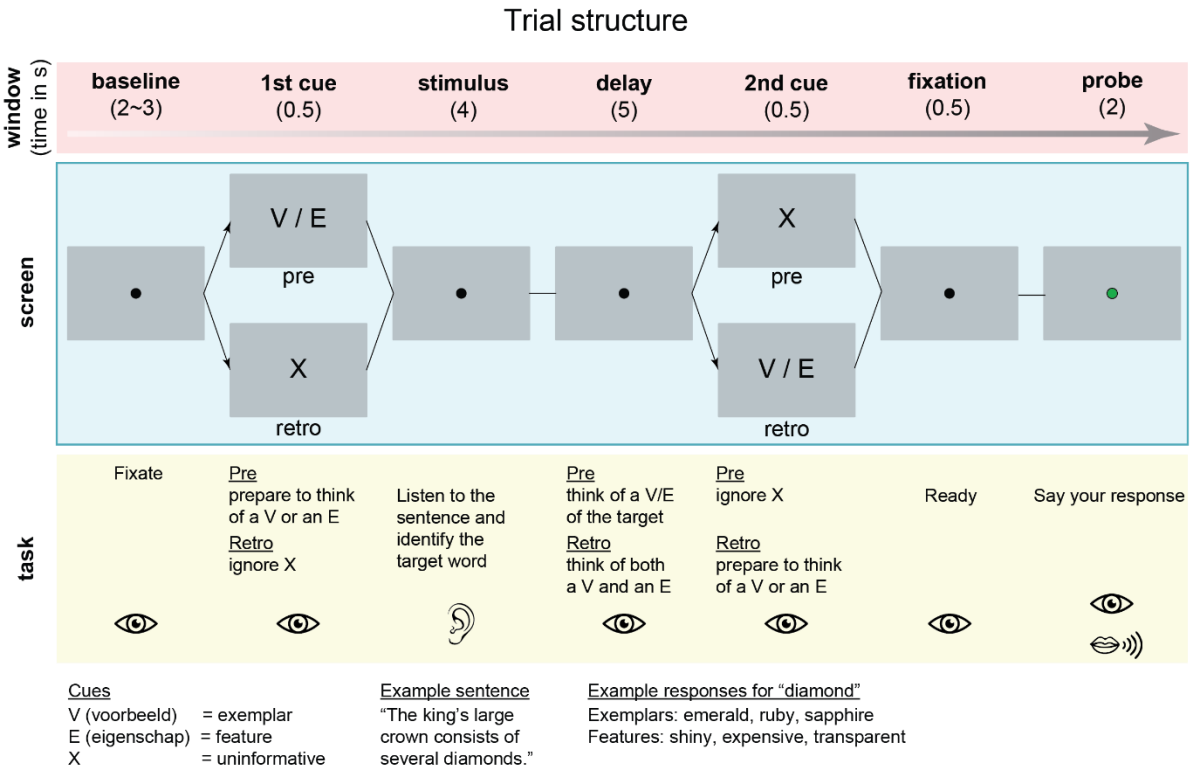
Abstract: Primate research has investigated the role of brain oscillations in basic cognitive functions. In particular, alpha oscillations are related to facilitated processing through the inhibition of task-irrelevant networks, while beta oscillations seem to carry content information about task rules. However, little is known about the generalization of fundamental operations to more complex processes. We constructed a novel rule-switching paradigm (see Figure) to study the role of alpha and beta dynamics during high-level processing. Dutch native speakers were required to come up with an exemplar or a feature of a target word embedded in spoken

sentences, based on a cue before (pre-cue) or after (retro-cue) listening to a sentence, and verbalized their answer at the end of the trial. Magnetoencephalography was recorded throughout. Reaction times of word production were longer for retro- compared to pre-cue, due to higher cognitive load, as well as for features compared to exemplars. Participants generated more diverse responses for features compared to exemplars, suggestive of increased association strength for exemplars. There was also a correlation between responses' word frequency and reaction times, potentially due to contextual constraint effects of the sentences. On the neural level, alpha power during the delay was lower for retro- compared to pre-cue in left hemispheric language regions. Critically, the power at each individual's peak alpha frequency negatively correlated with reaction times, in line with the role of alpha in facilitating task performance by regulating inhibition in regions linked to lexical retrieval. Furthermore, the spatiotemporal pattern of beta activity was dissociated between exemplars vs. features in right temporo-parietal regions, in line with the role of beta oscillations in the encoding of distinct categories. Overall, our study provides evidence for the generalizability of the role of alpha and beta oscillations from perceptual to complex processes, and offers a novel task to study rule-switching, working memory, and word production.



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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Topic: H.11. Language

Support: NIH Grant R01 DC019354
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Simons Collaboration on the Global Brain

Title: Critical language planning regions identified using direct electrical stimulation

Authors: *G. A. CASTELLUCCI[1], C. K. KOVACH[2], F. TABASI[2], D. CHRISTIANSON[2], J. D. W. GREENLEE[2], M. A. LONG[1];
[1]New York Univ. Neurosci. & Physiol., New York, NY; [2]Neurosurg., Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: Many brain areas have been linked to the planning of spoken language. In particular, we recently found that caudal regions of inferior frontal gyrus and middle frontal gyrus are active during speech preparation using intracranial electrocorticography (Castellucci *et al.*, 2022; *Nature*); however, whether such activity is critical for language planning is unknown. We used intracranial direct electrical stimulation to assay the contribution of 58 broadly sampled cortical sites across 23 neurosurgical patients in an interactive question-answer paradigm. We found that stimulation of 20 sites resulted in behavioral changes during task performance. Specifically, we observed that perturbation of 7 sites located within classical sensorimotor structures caused speech or facial-related sensorimotor effects (e.g., orofacial tetanus, gaze deviations). Meanwhile, stimulation of 9 other sites resulted in language planning deficits (i.e., longer reaction times, response errors), with 7 of these sites located in caudal inferior or middle frontal gyri - thus anatomically overlapping with our previously characterized planning region. We also found that stimulation of another 5 widely distributed sites in lateral cortex resulted in faster reaction times, suggesting stimulation-mediated improvements to cognitive function. In conclusion, we demonstrate that network dynamics within a compact frontal cortical region appears to be critical for speech preparation.

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Poster

PSTR113. Neural Circuits and Mechanisms of Language

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Program #/Poster #: PSTR113.23/UU25

Topic: H.11. Language

Support: NIH Grant R25NS065743
NIH Grant R01DC019653
NIH Grant U01NS121616

Title: Single-neuronal and laminar computations in the human prefrontal cortex during speech production

Authors: *W. MUNOZ[1], R. HARDSTONE[2], D. J. KELLAR[3], A. PAULK[2], M. JAMALI[1], I. CAPRARA[1], D. MESZENA[2], Y. KFIR[1], S. CASH[2], Z. WILLIAMS[1];
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Abstract: The neocortical column consists of a vast diversity of circuit elements and layers supporting a range of computations for cognitive functions. While much progress in our understanding of its architecture has been made in animal models, its implications for human cognitive processes, such as speech, remain undefined. To this end, we utilized Neuropixels - silicon-based electrophysiology recording probes with high channel count and recording site density - to measure neural activity with single-cellular resolution throughout the neocortical column and its layers. During recording, the participants (n = 4) performed a naturalistic sentence construction task that provided participants with pictorial representations of events that had to be verbally described in specific form and order. We then analyzed the activity of cortical neurons (n = 297 units), distributed throughout all cortical layers. We observed distinct spatiotemporal activity dynamics throughout the cortical column in the language-dominant prefrontal cortex that encoded a preparatory mode, as well as information about the words and sentences being constructed during natural speech. Furthermore, we observed the emergence of columnar activity patterns that tracked the specific linguistic components of speech production and that predicted behavioral performance during the task. Together, these results reveal a functional organization of the cortical column in the human prefrontal cortex subserving the production of speech, with implications for the design of a brain-machine interface approach for restoring language.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

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Program #/Poster #: PSTR114.01/UU26

Topic: H.13. Schizophrenia

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Title: Subchronic treatment with MK-801 during neonatal period decreased social interaction in adult rats

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Abstract: Glutamate and an ionotropic glutamate receptor subtype, N-methyl-D-aspartate (NMDA) receptor are essential for early brain development. Blockade of NMDA receptors with their antagonists during early postnatal period causes various neurological abnormalities. In addition, neonatal treatment with NMDA receptor antagonists induces behavioral abnormalities including deficits in sensorimotor gating, hypersensitivity to psychostimulants, and cognitive impairments. Since these abnormal behaviors resemble symptoms in schizophrenia, animals that received neonatal NMDA receptor blockade are considered useful model for schizophrenia. However, the effect of neonatal NMDA receptor blockade on social behavior is not fully understood. Therefore, we investigated the effects of neonatal treatment with MK-801, a non-competitive NMDA receptor antagonist, on social interaction in adult rats. Male rat pups received subcutaneous injection of 0.4 mg/kg MK-801 or saline twice a day from postnatal day (PND) 7 to 13. These rats were tested in reciprocal social interaction test at 9 weeks old. Subject rats were isolated for 4 hours before the test. In the test, subject rats were placed into an open field with a naïve rat and allowed to explore freely for 5 minutes. We measured the time spent in social interaction by the subject rats. As a results, rats neonatally treated with MK-801 showed significant decrease in social contacts compared to saline-treated rats. Next, we examined the effects of subchronic treatment with MK-801 in adulthood on social interaction. Another cohort of rats at 7 weeks of age were treated with MK-801 or saline for 7 days. Social interaction test was conducted 2 weeks after the treatment cessation. Unlike neonatal treatment, subchronic MK-801 treatment in adulthood did not affect social interaction. Since social behavior is known to be mediated by oxytocin system, we also investigated the effects of neonatal MK-801 treatment on the number of oxytocin neurons. We found that the number of oxytocin-immunoreactive neurons in the paraventricular hypothalamic nucleus of neonatally MK-801-treated rats did not differ from those of saline-treated rats. The results suggest that activation of NMDA receptors in early postnatal period is necessary for the development of social behavior. Impaired sociability is one of the core symptoms in schizophrenia. Thus, rats that received neonatal NMDA receptor blockade are useful for understanding the mechanism of social impairments in schizophrenia and development of novel therapeutic agents for it.

Disclosures: H. Furuie: None. **Y. Nakatake:** None.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.02/UU27

Topic: H.13. Schizophrenia

Support: P50 MH103222

Title: Biochemical and behavioral assessments of heterozygous mice with a reduction in kynurenine-3-monooxygenase ($Kmo^{+/-}$ mice)

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Abstract: Neuroactive metabolites of the kynurenine pathway (KP) of tryptophan degradation are believed to be involved in the pathophysiology of several psychiatric diseases, including schizophrenia (SZ) and bipolar disorder (BD). Kynurenic acid (KYNA) has received special attention in this regard since its levels are elevated in the brain and cerebrospinal fluid (CSF) of persons with SZ and may be causally related to the cognitive dysfunctions seen in the disease. Studies in rats had indicated that abnormally high KYNA levels in the fetal brain may cause pathophysiologically significant biochemical and behavioral changes in adulthood (Notarangelo and Pocivavsek, 2017; Beggiato et al., 2018). Notably, similar abnormal effects in adulthood are also seen after feeding pregnant C57Bl/6J mice either with the immediate KYNA precursor kynurenine (10 mg or 30 mg/day; "EKyn") compared with control mash ("ECon") from embryonic day (ED) 10/11 to ED 17/18 (Milosavljevic et al., SfN 2022). We now extended these studies to assess both basal differences and the postnatal consequences of this EKyn treatment in adult genetically modified heterozygous mice which have a reduced activity of kynurenine-3-monooxygenase (KMO), the enzyme that is impaired in people with SZ (Sathyasaikumar et al., 2011) and known to regulate KYNA levels (Kmo+/- mice). Microdialysis, performed in the prefrontal cortex on postnatal day (PD) 56, revealed significantly higher basal KYNA levels in Kmo+/- (0.45 ± 0.03 nM) than in wild-type (0.26 ± 0.03 nM) mice ($P<0.001$, Student's t-test). Tested behaviorally in the Barnes maze, the latency to enter the escape box was found to be significantly higher in adult male Kmo+/- mice than in wild-type mice (2-way ANOVA, $P<0.05$). Male Kmo+/- mice also took longer to find the escape box when it was moved to an alternate location during the reversal trial ($P<0.01$), indicating impaired prefrontal-mediated reversal learning. Adult (PD 65-80) offspring of Kmo+/- dams that had received 50 mg (but not 10 or 30 mg) kynurenine/day from ED 10/11 to ED 17/18 showed a significant elevation in extracellular KYNA in the prefrontal cortex ($P<0.001$, Student's t-test). Administration of the potent, specific kynurenine aminotransferase II inhibitor PF-04859989 (30 mg/kg, s.c.) resulted in a rapid and significant decrease in extracellular KYNA levels in these EKyn Kmo+/- offspring (2-way ANOVA, $P<0.001$ at peak effect). Taken together, our results suggest that Kmo+/- mice provide an improved animal model for studying the role of KYNA in the etiology of neuropsychiatric illnesses.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.03/UU28

Topic: H.13. Schizophrenia

Support: KAKENHI 16H05373.

Title: Schizophrenia-like behavior in the D1R-specific NSF deficient mice

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Abstract: Dysregulated dopaminergic modulation in the striatal and prefrontal function is fundamental to many models that seek to explain the mechanisms underlying the symptoms of schizophrenia. Although binding of radioligand to the dopamine D1 receptor (D1R) was reduced in the prefrontal cortex of schizophrenics, it remains unclear whether these are causal relationship between prefrontal cortex and striatal pathology. As previous report has already shown that N-ethylmaleimide sensitive factor (NSF) expression is reduced in postmortem brain tissue of schizophrenic patients. NSF interacts with D1R and regulates the localization of D1R. In the present study, we generated the D1R-specific NSF conditional knockout mice (D1R-NSFcKO) and investigated their behavioral, neurotransmitter, and neurophysiological phenotypes in vivo. D1R-NSFcKO mice exhibited the abnormal spontaneous rotation behaviors and high locomotion activity. The dopamine D2 receptor antagonist sulpiride suppressed the hyperactive in D1R-NSFcKO mice. Since early psychosis studies suggest that prepulse inhibition (PPI) disruption is present before the onset of psychosis. We investigated the startle habituation and PPI test, and found that both startle habituation and PPI were impaired in D1R-NSFcKO mice. In addition, to investigate whether dopamine abnormalities in the striatum, we used the HPLC-ECD analysis. We found that dopamine was significantly increased in the striatum of D1R-NSFcKO mice compared with that of control mice. These findings demonstrate that NSF plays a role in motor activation and sensorimotor gating via regulating the dopamine and dopamine receptor. D1R-NSFcKO mice exhibited locomotor up-regulation and a defect in sensorimotor gating, resembling the behavioral phenotype of schizophrenia.

Disclosures: M. Xie: None. **K. Murata:** None. **H. Matsuzaki:** None.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

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Program #/Poster #: PSTR114.04/VV1

Topic: H.13. Schizophrenia

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Japan Society for the Promotion of Science (JSPS) KAKENHI (20H03428, 20K07082)
JST SPRING, Grant Number JPMJSP2125

Title: A novel mouse model of schizophrenia with exonic deletion of Reln gene

Authors: *Y. ZHU[1], Y. TSUNEURA[4], M. SAWAHATA[1], A. SOBUE[1], T. NAGAI[5], H. MIZOGUCHI[1], D. MORI[2,3], T. NABESHIMA[6], N. OZAKI[7], K. YAMADA[1];
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Abstract: Reelin, an extracellular matrix glycoprotein, is critical for cortical layer formation during brain development and has been implicated in various psychiatric disorders, including schizophrenia (SCZ). We have previously identified a novel exonic deletion in the RELN gene in an SCZ patient, encompassing exons 52 to 58. To elucidate pathophysiological role of this exonic deletion in SCZ, we have generated transgenic mice (Reln-del) carrying the identical RELN deletion discovered in a Japanese schizophrenia patient using the CRISPR/Cas9 method.In order to elucidate the pathophysiological implications of RELN gene deletion found in SCZ, behavioral and brain structure analyses were carried out in Reln-del mice. Homozygous Reln-del mice displayed a phenotype reminiscent of reeler mice, characterized by cerebellar atrophy, dysplasia of cerebral layers, and reduced levels of cerebral Reelin protein. In heterozygous Reln-del mice, reelin expression level was approximately half of that in wild-type (WT) mice. In the three-chamber social interaction test, heterozygous Reln-del mice revealed impaired social novelty. To gain insights into the underlying brain dysfunction, we performed both in vitro and in vivo analyses. Firstly, primary cultured cortical neurons from Reln-del mice exhibited a significant reduction in neurite length, branch point numbers, and postsynaptic density protein 95 (PSD95) immunoreactive puncta as compared to those in WT mice. Furthermore, we conducted an in vivo spine morphology analysis in the medial prefrontal cortex (mPFC) of WT and Reln-del mice. A significant decrease in excitatory dendrite spine density was observed in the mPFC layers II/III and V of Reln-del mice compared to WT mice. Especially, there was a marked reduction in the number of stubby, mushroom, and filopodia spines.Collectively, our findings with the novel Reln-del mice have significant implications for the development of reelin-based therapies for SCZ.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

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Topic: H.13. Schizophrenia

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UC Davis Conte Center (P50 MH106438)
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Title: Baseline immunoreactivity before pregnancy predicts susceptibility and resilience to aberrant behaviors across multiple domains in offspring following maternal immune activation

Authors: *K. PRENDERGAST[1], C. N. MCCORMACK[2], V. FLORES[2], E. CONNOLLY[2], C. A. KELLAND[3], J. SCHAUER[3], L. HAAPANEN[3], M. PARK[2], C. CHEN[2], M. AGUILAR[2], B. CHOJOLAN[2], M. SIMAFRANCA[5], J. PADDA[5], A. KAUSHIK[5], A. RAZA[5], M. SCHWIEDER[5], C. S. CARTER[6], M. BAUMAN[7], A. IOSIF[4], J. VAN DE WATER[8], K. A. MCALLISTER[2];
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Abstract: Viral infections during pregnancy are associated with increased risk of neurodevelopmental (NDD) and psychiatric disorders in offspring. The viral mimic, poly(I:C), causes maternal immune activation (MIA) in mouse models leading to neuroanatomical and behavioral phenotypes in offspring in domains similar to those found in human disorders. Despite the potential of MIA rodent models to identify new biomarkers and therapeutic interventions for a range of NDD and psychiatric disorders, current approaches ignore two of the most critical aspects of this risk factor for human disease: (i) most pregnancies are resilient to maternal viral infection and (ii) susceptible pregnancies can lead to different combinations of phenotypes in offspring. Previously, we discovered that young isogenic female mice exhibit a wide range of baseline immunoreactivity (BIR) before pregnancy, as determined by the level of serum interleukin-6 collected 2.5 hours following a low dose poly(I:C) injection (5mg/kg). Notably, we reported that BIR before pregnancy and the poly(I:C) dose used to induce MIA together predict resilience and susceptibility of offspring to repetitive and exploratory behavioral alterations. In this study, we aimed to determine if a broader range of cytokines might predict resilience and susceptibility of offspring to altered affective, social, and cognitive behaviors following MIA. First, a time-course analysis of 31 cytokines was conducted at 2.5, 6 and 24 hours following intraperitoneal injection of 5mg/kg poly(I:C) (n = 72) or saline (n = 36) into young virgin female C57BL/6J mice. Then, 78 BIR- and age-matched female mice were injected at mid-gestation (E12.5) with saline or poly(I:C) to induce MIA. An extended behavioral battery

to assess anxiety,
repetitive behavior, cognition, memory, social behavior, and conditioned fear was conducted in juvenile and young adult offspring (n = 330). We found that BIR is defined by a wide range of pro-inflammatory, anti-inflammatory, and regulatory cytokines at 2.5, 6 and 24 hours following poly(I:C) injection before pregnancy. Moreover, these patterns of BIR interact with gestational poly(I:C) dose to predict susceptibility and resilience of offspring to elevated repetitive behavior and social deficits in offspring in a sex-dependent manner. Ongoing experiments continue to assess whether the dynamic gestational immune response following MIA differs between dams with distinct BIR profiles, and whether these patterns of gestational immune signaling predict which offspring will be most at risk for distinct clusters of behavioral perturbations following MIA.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

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Program #/Poster #: PSTR114.06/VV3

Topic: H.13. Schizophrenia

Support: NIH Grant MH043784
NIH Grant MH117089

Title: Synaptic alterations in genetically-silenced pyramidal neurons from monkey prefrontal cortex

Authors: *G. GONZALEZ-BURGOS[1], T. MIYAMAE[1], Y. NISHIHATA[1], O. L. KRIMER[1], K. N. FISH[1], Z.-L. CAI[2], M. XUE[2], W. R. STAUFFER[1], D. A. LEWIS[1];
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Abstract: Schizophrenia is associated with fewer dendritic spines, the site of most excitatory inputs, on pyramidal neurons (PNs) in layer 3 of the dorsolateral prefrontal cortex (DLPFC). These deficits are thought to originate developmentally and to reflect impairments in early synaptogenesis and/or later synaptic pruning. The spine deficits in schizophrenia are thought to reduce the excitatory drive to PNs, causing them to be hypoactive. However, the impact of PN hypoactivity during adolescence on the properties of excitatory synapses on DLPFC PNs is unknown. Here, we used a genetic silencing approach to test whether hypoactivity affects synaptic properties in PNs from the DLPFC of periadolescent (2.6 to 4.7 year-old) rhesus monkeys. We microinjected *in vivo* a combination of viral vectors to overexpress inward rectifier

Kir2.1 K+ channels, a manipulation that reduces neuronal excitability and *in vivo* firing activity in the mouse sensory cortex (Xue et al. *Nature* 2014). Since genetic silencing has not been applied to the primate cortex, to confirm the effectiveness of the manipulation we characterized the excitability of DLPFC PNs in acute slices prepared after 6-8 weeks of Kir2.1 overexpression *in vivo*. We found that PNs overexpressing Kir2.1 K+ channels had a more negative resting membrane potential, lower input resistance, and higher rheobase current, which in combination produced a substantially reduced excitability. PNs overexpressing Kir2.1 did not differ from neighboring PNs in dendritic tree architecture or dendritic spine density or in $GABA_AR$-mediated sIPSCs. In contrast, Kir2.1 overexpression reduced the sEPSC mean amplitude and produced a leftward shift in the sEPSC amplitude distribution, both consistent with decreased strength of excitatory synapses onto PNs. Interestingly, the degree of change in excitatory synaptic strength and the magnitude of Kir2.1 effect on PN excitability were not correlated, suggesting that the changes in sEPSC amplitude partly involve a presynaptic effect. Our data suggest that reducing PN excitability *in vivo* produces a decrease in excitatory synaptic strength, but without significantly affecting inhibitory synapses, onto PNs. These results suggest that, if the deficit of axospinous synapses in schizophrenia produces hypoactivity during the periadolescence period, then this deficit would decrease the strength of the excitatory synapses that persist in the affected PNs.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

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Topic: H.13. Schizophrenia

Support: 5T32MH018870
R01MH080234
5R01MH124923

Title: Utilizing widefield calcium imaging to evaluate intrinsic in vivo cortical network dynamics in wildtype and schizophrenia genetic risk model mice

Authors: *E. M. PARKER[1], S. SAXENA[3,4], D. S. PETERKA[2], J. A. GOGOS[2]; [2]Zuckerman Inst., [1]Columbia Univ., New York, NY; [3]Univ. of Florida, Gainesville, FL; [4]Yale Univ., New Haven, CT

Abstract: Widefield calcium imaging is a non-invasive imaging technique used to measure neural activity with high spatiotemporal resolution across large areas of superficial murine cortex. This technique combines the many of the advantages of popular non-invasive techniques

like fMRI and EEG, with the potential for cell-type specificity. It is also relatively cheap and straightforward to implement. The data is collected at fast time scales, with relatively high signal-to-noise and during various behavior states such as ambulation and whisking. We apply multiple image processing and analysis pipelines that include temporal smoothing and hemodynamics correction, as well as automated signal extraction using LocaNMF and have begun to evaluate mesoscale calcium activity in wildtype and schizophrenia genetic risk model mice. As resting-state connectivity is disrupted in schizophrenia patients, we predict that similar deficits may be present in mice carrying homologs to highly penetrant human genes. In other studies, we and others previously reported working memory and circuit deficits in a mouse model of SETD1A, a critical schizophrenia risk gene. For the current study, we hypothesized that male and female SETD1A haploinsufficient mice should exhibit abnormal intrinsic/ "resting-state" functional connectivity in superficial cortical brain regions. Continuing this exploration, we are pursuing more sophisticated functional connectivity analyses including utilizing LocaNMF defined regions, which map to the Allen Atlas, providing harmonized regions for comparison across the different cohorts. These developments will lead to a greater understanding of intrinsic activity observable using the emerging technique of widefield calcium imaging and help establish widefield calcium imaging as an important translatable methodology for studying network mechanisms underlying cognitive impairments in risk models for mental illness or neurological disease.

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Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.08/VV4

Topic: H.13. Schizophrenia

Title: Identification of a rat model of schizophrenia and platform-based in vivo assays to investigate synaptic deficits in CNS disorders

Authors: *M. HOFMANN[1], H. ZHOU[1], T. W. ROSAHL[1], N. SACHS[1], G. PAVLOVIC[2], L. LINDNER[2], D. LOVATT[1], Y. WANG[1], M. PURCELL[1], X. WANG[1], M. MARINO[1]; [1]Merck, West Point, PA; [2]Inst. Clinique De La Souris (ICS), Inst. Clinique De La Souris (ICS), Illkirch, France

Abstract: The synapse, which is the point of chemical communication between neurons, requires a presynaptic axon terminal near a postsynaptic specialization to allow for the flow of information through the release of neurotransmitters and activation of postsynaptic receptors. Postsynaptic dendritic spines, the major sites of excitatory glutamatergic synaptic transmission, are highly dynamic and morphologically diverse structures and are considered key building blocks underlying learning and memory. Synaptic deficits are observed in many CNS diseases including schizophrenia and Alzheimer's disease, and consequently, identifying and validating

targets that rescue synaptic deficits has the potential to provide novel therapeutic approaches for multiple CNS disorders. We are interested in building assays to interrogate synaptic density in vivo that can be used to support multiple targets of interest. These assays can be used to characterize transgenic rodent models (are there synapse deficits?) and ultimately to validate whether a specific target of interest can ameliorate synaptic loss in vivo. Here, we focused on assay development in a rat model of the 15q13.3 microdeletion in humans which is associated with increased risk for the development of neuropsychiatric conditions including schizophrenia, epilepsy, and cognitive impairment. Several approaches were used to assess synapses in this model including immunohistochemical quantification of presynaptic and postsynaptic markers, the Golgi-stain method to directly measure spine density and morphology, and a clinically relevant SV2A PET tracer to evaluate synaptic density in vivo. A robust spine deficit was observed in the 15q13.3 rat model using the Golgi-stain enabling the model for future efficacy studies using disease modifying therapeutic approaches. In addition, the pilot studies with the SV2A PET tracer suggested decreased SV2A PET signal in homozygous rats demonstrating a path forward with this translational biomarker. Overall, we identified platform-based assays that can be used across synaptogenesis targets and provided a roadmap for the identification of other models of synaptic deficits.

Disclosures: **M. Hofmann:** A. Employment/Salary (full or part-time):; Merck. **H. Zhou:** A. Employment/Salary (full or part-time):; Merck. **T.W. Rosahl:** A. Employment/Salary (full or part-time):; Merck. **N. Sachs:** A. Employment/Salary (full or part-time):; Merck. **G. Pavlovic:** A. Employment/Salary (full or part-time):; Institut Clinique De La Souris (ICS). **L. Lindner:** A. Employment/Salary (full or part-time):; Institut Clinique De La Souris (ICS). **D. Lovatt:** A. Employment/Salary (full or part-time):; Merck. **Y. Wang:** A. Employment/Salary (full or part-time):; Merck. **M. Purcell:** A. Employment/Salary (full or part-time):; Merck. **X. Wang:** A. Employment/Salary (full or part-time):; Merck. **M. Marino:** A. Employment/Salary (full or part-time):; Merck.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.09/VV5

Topic: H.13. Schizophrenia

Title: Characterization of SUVN-2206043: Dual 5-HT1A agonist and 5-HT2A antagonist ligand in animal models of depression and psychosis

Authors: *R. ABRAHAM, S. PETLU,, R. SUBRAMANIAN, R. MEDAPATI, P. JAYARAJAN, J. THENTU, V. BENADE, R. BADANGE, K. BOJJA, A. MOHAMMED, A. SHINDE, S. MANCHINEELLA, T. NARASIMHULA, R. NIROGI;
Suven Life Sciences, Ltd., Hyderabad, India

Abstract: Targeting the serotonergic system and its various receptors is a widely pursued option for the treatment of schizophrenia and the associated positive and negative symptoms. SUVN-2206043 is a new chemical entity that targets the 5-HT_{1A} and 5-HT_{2A} receptors. SUVN-2206043 has been evaluated for its binding and functional activity using radioligand binding assay and GTPgS cell based functional assays. The pharmacokinetics of SUVN-2206043 were assessed in Wistar rats and Beagle dogs (n=3-4/group). Receptor occupancy at 5-HT_{1A}, 5-HT_{2A} and dopaminergic D_2 receptors were evaluated in Wistar rats using non-radiolabeled tracers (n=4/group). Assessment of SUVN-2206043 for its antipsychotic - like effects in Wistar rats was carried out in the open field test using either MK-801 or amphetamine challenge (n=8/ group). Here, olanzapine was used as a positive control in the open field test. SUVN-2206043 was assessed for its antidepressant - like properties in a mice forced swim test (n=8/group), with imipramine as a positive control. The data from the open field, and forced swim tests were compared using one-way ANOVA followed by Dunnett's test. SUVN-2206043 was assessed for its potential to induce motor impediment in Wistar rats using the rotarod test (n=8). Based on the pharmacokinetics of SUVN-2206043, the latency to fall from the rotarod was measured at regular intervals. The data from this assay were compared using two-way ANOVA followed by Dunnett's test. From the in-vitro binding assay, SUVN-2206043 was found to have affinity for 5-HT_{2A} and 5-HT_{1A} receptors with minimal affinity for dopamine D_2 receptors. Functionally, SUVN-2206043 is an antagonist at the 5-HT_{2A} receptor and an agonist at 5-HT_{1A} receptor. SUVN-2206043 was found to have receptor occupancy for 5-HT_{2A} and 5-HT_{1A} receptors in rats. SUVN-2206043 was found to be orally bioavailable both in rats and dogs with adequate brain penetration properties. SUVN-2206043 attenuated MK-801 as well as amphetamine induced hyperlocomotor activity in the open field. SUVN-2206043 reduced the duration of immobility in the forced swim test. SUVN-2206043 did not induce motor impediment at the tested doses. In conclusion, SUVN-2206043 was found to be a dual serotonin 5-HT_{2A} receptor antagonist and a 5-HT_{1A} agonist ligand that exhibited antipsychotic and antidepressant like effects and was devoid of motor impediments.

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Petlu,:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Thentu:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **K. Bojja:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Manchineella:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **T. Narasimhula:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.10/VV6

Topic: H.13. Schizophrenia

Title: Enhanced in vivo firing in chemogenetically identified dopamine midbrain neurons projecting to the dorsal striatum in freely moving 22q11.2 deletion syndrome mice, a genetic model of Schizophrenia

Authors: *S. BIKAS, J. ROEPER, A. DIAMANTOPOULOU;
Inst. of Neurophysiol., Johann Wolfgang Goethe-University, Frankfurt am Main, Germany

Abstract: Dopamine (DA) dysregulation has been a central hypothesis of schizophrenia (SCZ) psychopathology for decades, but updates from clinical in vivo imaging studies demonstrating DA elevation within nigrostriatal pathways, reorient the focus to the dorsal striatum as primary region for the pathophysiology of SCZ. To study DA abnormalities relevant to human disease, we made use of the *Df(16)A*$^{+/-}$ mouse model of the 22q11.2 Deletion Syndrome. The hemizygous microdeletions of the 22q11.2 locus pose the highest genetic risk factor for the development of SCZ, representing ~ 30%- fold increase over the general population risk of 1%. Here, we looked at the function of the DA midbrain system as a source of DA dysregulation relevant for SCZ. Initially, we characterized the electrical *in vivo* properties of pharmacologically identified DA midbrain neurons by chronic *in vivo* single-unit extracellular recordings during open field exploration in awake freely moving male and female *Df(16)A*$^{+/-}$ mice and wild type littermates. We detected persistent electrophysiological hyperactivity in DA neurons in the medial substantia nigra (mSN) in both male and female *Df(16)A*$^{+/-}$ mice in comparison to controls. This was characterized by increased firing frequencies (median FR: WT: 4.35 Hz; *Df(16)A*$^{+/}$: 7.51 Hz; p = 0.0002) and elevated bursting activity (median SFB: WT: 40.3, n = 53, N = 7; *Df(16)A*$^{+/-}$: 71.5, n= 97, N= 7; p < 0.0001). DA bursting hyperactivity was also persistent in the lateral SN of male *Df(16)A*$^{+/-}$ mice compared to controls (median SFB: WT: 58.0, n = 33, N = 3; *Df(16)A*$^{+/-}$: 73.5, n= 31, N= 3; p < 0.0025). On the contrary, *in vivo* recordings of DA neurons in the ventral tegmental area (VTA), the main source of the mesolimbic dopamine system, revealed no differences between *Df(16)A+/-* and controls (median FR: WT: 7.21 Hz & SFB: 61.8, n = 107, N = 7; *Df(16)A*$^{+/-}$ median FR: 7.46 Hz & SFB 61.2, n= 151, N= 7). Moreover, by use of chemogenetic (100 µg/kg Deschloroclozapine) mediated inhibition via hM4D(Gi) DREADD expression in DAT-Cre X *Df(16)A+/-* mice we specifically assessed activity of the DMS-projecting mSN DA subpopulation. Our results showed persistent DA hyperactivity (median FR: DAT-Cre: 5.00 Hz; DAT-Cre X *Df(16)A+/-* : 7.13 Hz; p = 0.0007) and elevated bursting activity (median SFB: DAT-Cre: 43.7, n = 21, N= 5; DAT-Cre X *Df(16)A+/-* : 59.5, n = 36, N = 5; p < 0.0001). In summary, our findings reveal an ubiquitous hyperactive phenotype of DA neurons in the 22q11 mouse model, with increased bursting activity, even in selective subpopulations such as the DMS-projecting DA mSN neurons.

Disclosures: S. Bikas: None. **J. Roeper:** None. **A. Diamantopoulou:** None.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.11/VV7

Topic: H.13. Schizophrenia

Support: CONACYT Grant 320520

Title: Gestational exposure to Toxoplasma gondii proteins induces cognitive alterations in adult rats by increasing KYNA levels in the hippocampus

Authors: *T. BLANCO AYALA[1], A. ACOSTA RAMIREZ[2], S. MUÑIZ HERNÁNDEZ[3], E. ROMERO NUÑEZ[4], B. PINEDA[5], V. PEREZ DE LA CRUZ[6];
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Abstract: An association between maternal gestational *Toxoplasma gondii* (T. gondii) infection and an increased risk of progeny developing schizophrenia (SQZ) in adulthood has been shown in previous studies. Alterations in dopamine and glutamate levels have been described in patients with SQZ. These neurotransmitters can be regulated by tryptophan (Trp) metabolites through the kinurenine pathway (KP) and have an effect on cognition. In this study we evaluate the neurochemical and behavioral effects of gestational exposure to *T. gondii* proteins. Adult female Wistar rats were divided into 3 groups: 1) Control; 2) PG, pre-gestationally immunized with T. gondii (100 µg protein, once weekly for 3 weeks pre-gestation) and 3) G18, immunized at gestational day 18. At postnatal day 60, cognitive and behavioral alterations of the progeny were assessed using the novel object recognition test (NOR) and Crawley test. Brain levels of glutamate, dopamine, kynurenic acid (KYNA) and 3-hydroxykinurenine (3-HK) were measured by HPLC with electrochemical and fluorescence detection. In the NOR test, G18 and PG groups could not discriminate between the novel object and the familiar object. When assessing social behavior and memory using the Crawley test, the G18 group was unable to distinguish an unfamiliar animal from a familiar one when assessing long-term memory. Dopamine and glutamate levels decreased more markedly in the G18 group; whereas hippocampal KYNA levels were elevated in both groups, 3-HK levels increased only in the cortex of the G18 group. Previous evidence has shown that prenatal infection may cause maternal immune activation (MIA) and enhance risk of schizophrenia in the offspring. Here we showed that gestational exposure, GD18, to *T. gondii* proteins induced behavioral changes in the adult offspring (PD60) caused by a marked decrease in dopamine and glutamate levels. Increased levels of KYNA and 3HK in these same brain tissues suggest a possible mechanism that would explain the reduction of both neurotransmitters. Gestational exposure to T. gondii proteins probably activates microglia and astrocytes thus stimulating the KP with neuromodulatory effects on neurotransmission finally leading to long-term memory disruption and social behavior impairments in the offspring.

Disclosures: **T. Blanco Ayala:** None. **A. Acosta Ramirez:** None. **S. Muñiz Hernández:** None. **E. ROMERO Nuñez:** None. **B. Pineda:** None. **V. Perez De La Cruz:** None.

Poster

PSTR114. Animal Models Relevant to Schizophrenia

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR114.12/VV8

Topic: G.08. Other Psychiatric Disorders

Support: NHRI-EX112-11114NI
MOST 111-2320-B002-045

Title: Gabra6-containing receptor as a novel therapy target for attention-deficit hyperactivity disorder: a proof-of-concept study in MK-801-treated juvenile mice

Authors: C.-C. LU[1], H.-J. LEE[1], A. MOURI[3], D. SHARMIN[5], J. M. COOK[5], W. SIEGHART[6], T. NABESHIMA[4], ***L.-C. CHIOU**[2,1];
[1]Grad. Inst. of Pharmacology, Col. of Med., [2]Grad. Inst. of Brain and Mind Sci., Natl. Taiwan Univ., Taipei, Taiwan; [3]Dept. of Reg. Sci., Grad. Sch. of Hlth. Sci., [4]Lab. Hlth. Med. Sci. Innovation, Grad. Sch. of Hlth. Sci., Fujita Hlth. Univ., Toyoake, Japan; [5]Dept. of Chem. and Biochem., Univ. WI-Milwaukee, Milwaukee, WI; [6]Ctr. For Brain Res., Med. Univ. Vienna, Vienna, Austria

Abstract: The α6 subunit-containing $GABA_A$ receptors (α6$GABA_A$Rs) are densely expressed in granule cells of the cerebellum, which has been implicated in the pathogenesis of attention-deficit hyperactivity disorders (ADHD). Due to the lack of selective ligands for α6$GABA_A$Rs, their pathophysiological role(s) were largely unknown. We have identified a series of pyrazoloquinolinones (PQs) as the α6$GABA_A$R-selective positive allosteric modulators (PAM).[1] In this study, using PQ Compound 6 and α6$GABA_A$R-selective antagonist, furosemide as pharmacological tools and mice lacking *Gabra6*, the gene encoding the α6 subunit of $GABA_A$Rs, we explored the role of α6$GABA_A$Rs in the pathogenesis of ADHD. Male ICR mice, at P28, when being treated with MK-801 (0.2 mg/kg, i.p.), an NMDA channel blocker, displayed behavioral phenotypes mimicking the three core symptoms of ADHD, i.e. hyperlocomotion, impulsivity, and inattention. They were evidenced, respectively, by the increased locomotor activity in the open-field test, shorter latency and higher frequency of jumping events in the cliff avoidance reaction test, and decreased exploratory preference in the novel object recognition test. Compound 6 (3 mg/kg, i.p.) significantly prevented MK-801-induced hyperlocomotion, impulsivity, and impaired attention in juvenile male mice with an efficacy comparable to atomoxetine, an ADHD medication. The rescue effects of Compound 6 were prevented when furosemide was intra-cerebellarly pre-administered and were nullified in *Gabra6* knockout mice. SCH23390, a dopamine D1 receptor antagonist, when given by bilateral intra-prefrontal cortex (PFC) microinjection (0.1 μg/side), also mimicked the rescue effects of Compound 6 on the three core symptom-like behaviors in this ADHD model. Intra-PFC SCH23390, when pre-

administered before Compound 6, occluded the rescue effects of Compound 6 on hyperlocomotion and impulsivity, but not inattention. These results suggest Compound 6 exerts its rescue effects, at least partially, by acting as a PAM of cerebellar α6GABAARs, via mechanism(s) other than directly blocking D1 receptor-mediated transmission in the PFC. Thus, α6GABA$_A$R-selective PAMs, like PQ compounds, are potential therapeutic drug candidates for ADHD.[1]Knutson et al (2018) J Med Chem 61:2422.

Disclosures: C. Lu: None. **H. Lee:** None. **A. Mouri:** None. **D. Sharmin:** None. **J.M. Cook:** None. **W. Sieghart:** None. **T. Nabeshima:** None. **L. Chiou:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.01/VV9

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: ZIAMH002881

Title: A split-GFP based cellular assay to screen for modulators of mitochondrial fission

Authors: D. PANJA[1], ***Z. LI**[2];
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Abstract: A split-GFP based cellular assay to screen for modulators of mitochondrial fission Debabrata Panja and Zheng LiSection on Synapse Development Plasticity, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20912, USA.Mitochondria undergo dynamic changes, altering their shapes through fusion and fission processes in response to cellular requirements. These processes are regulated by various proteins, including Opa-1, Mitofusin-1, and Mitofusin-2 which facilitate fusion, and cytosolic dynamin-related protein 1 (Drp1) and its receptors (Mff, Fis1, MiD49, MiD51) which control fission. The dynamic nature of the mitochondrial network has been explored using time-lapse imaging of mitochondria tagged with fluorescent proteins in live cells. In this study, we developed a split-GFP based system to detect mitochondrial fission sites. We fused a larger GFP fragment (GFP1-10) with Drp1 and a smaller GFP fragment (GFP11) with Mid51, a Drp1 receptor on mitochondria. The two GFP fragments are not fluorescent. When Drp1 binds to Mid51 during mitochondrial fission, the two GFP fragments attached to them are reconstituted to fluorescent proteins. We tested the efficacy of this system in Hela cells. We treated cells transfected with the split-GFP fission detector to induce mitochondrial fission with sublethal concentrations of complex I and V inhibitors or H_2O_2. There is an increase in mitochondrial fragmentation and the number and brightness of GFP puncta after treatment. These results indicate that the split-GFP system can be adapted to visualize mitochondrial fission in live cells. This approach can be potentially used to discover novel modulators of mitochondrial dynamics.

Disclosures: **D. Panja:** None. **Z. Li:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.02/VV10

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NSF Award # 2152260
Searle Scholars Program #SSP-2022-107
Burroughs Wellcome Fund Career Award #1019469

Title: An activity-dependent enzyme for rapid and stable tagging of neural ensembles in vivo

Authors: *R. ZHANG[1,2,3], M. ANGUIANO[2,3,4], S. LIN[2,3], I. K. AARRESTAD[4,5,6], J. CHANDRA[2,3,4], S. VADDE[2,3], D. E. OLSON[2,5,6,7], C. K. KIM[2,3];
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Abstract: Recent technological advancements have revolutionized our ability to study the brain at the cellular and molecular levels. However, the ability to rapidly and stably tag functionally co-activated neurons deep within the brain remains a challenge. Traditional reporter gene expression methods like c-FOS suffer from low temporal resolution and specificity due to the imprecise onset of transcriptional activation upon neuron activity. Therefore, there is an immediate need to develop new techniques to tag and isolate specific subpopulations of neurons activated by external stimuli. Here, we engineered a Calcium-dependent split-TurboID (CaST) enzyme for rapid and non-invasive neural activity mapping. The CaST is derived from the biotin ligase TurboID, which covalently attaches a biotin labeling molecule onto itself and adjacent proteins. TurboID can already be split into two inactive fragments to detect static protein-protein interactions between two subcellular locations. We re-engineered split-TurboID to detect dynamic changes in intracellular calcium concentration. We fused each half of the split-TurboID to Calmodulin or MKII (two calcium-dependent interaction partners) and anchored the fragments to the membrane or in cytosol. Upon neuronal activation and calcium influx, split-TurboID will reconstitute and label proximal proteins in the presence of biotin. Biotinylated proteins can be visualized using streptavidin-Alexa Fluor 647 (SA-647; which binds biotin) or pulled down using streptavidin beads. We characterized the specificity and temporal properties of CaST in vitro. We then performed an in vivo demonstration of CaST by expressing it in the medial prefrontal cortex (mPFC) of mice to tag psilocybin-activated neurons. Histological analysis confirmed that CaST was properly expressed in neurons, and we observed robust SA-647 labeling only when both biotin and psilocybin were injected, as opposed to controls without psilocybin. Quantitative analysis demonstrated an increasing ratio of SA-647/GFP fluorescence in mice treated with psilocybin (2.1±0.10) compared to controls (1.4±0.06; n=8 slices from 3

mice, each group). Additionally, psilocybin-treated mice had a higher fraction of neurons with a SA-647 intensity over the threshold than control (0.72±0.086 vs. 0.12±0.026). These findings describe CaST as a novel technology for rapid and non-invasive detection of acutely activated neurons in vivo. We envision that CaST may be applied in cultured cells and intact tissues across different models and species. Future proteomic analysis within CaST-labeled neurons may lead to the discovery of activity-induced signaling pathways.

Disclosures: R. Zhang: None. **M. Anguiano:** None. **S. Lin:** None. **I.K. Aarrestad:** None. **J. Chandra:** None. **S. Vadde:** None. **D.E. Olson:** None. **C.K. Kim:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.03/VV11

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Burroughs Wellcome Fund Career Award #1019469
Brain and behavior Research Foundation Young Investigator Award #30238
Searle Scholars Program #SSP-2022-107
CIHR Post-Doctoral Training Award #202210MFE-491520-297096
UC Davis BHCOE Pilot Award

Title: Re-activation of a psychedelic neural signature reduces anxiety-like behavior

Authors: *S. LIN[1,2], J. MUIR[1,2], I. AARRESTAD[3,4,5,6], H. R. DANIELS[1,2], J. MA[1,2], L. TIAN[4], D. E. OLSON[1,4,5,6], C. K. KIM[1,2];
[1]Ctr. for Neurosci., [2]Dept. of Neurology, Sch. of Med., [3]Neurosci. Grad. Program, [4]Dept. of Biochem. & Mol. Medicine, Sch. of Med., [5]Dept. of Chem., [6]Inst. for Psychedelics and Neurotherapeutics, Univ. of California, Davis, Davis, CA

Abstract: Psychedelics have gained an enormous amount of attention in recent years due to their therapeutic potential for treating neuropsychiatric disorders such as depression and anxiety. These drugs are known to bind serotonergic 5-HT2A receptors, driving functional and structural changes in the prefrontal cortex (PFC), a region heavily implicated in the pathophysiology of these disorders. However, little is known about the precise circuit mechanisms of these drugs. We asked how 2,5-dimethoxy-4-iodoamphetamine (DOI), a 5-HT2A receptor agonist, modulates PFC activity in order to drive behavioral change. Behaviorally, DOI reduces anxiety-like behavior in both sexes in the Marble Burying Test (MBT) 30 minutes post-injection (Females: n=10,10, $p<0.0001$; Males: n=10,10, $p<0.0001$,) and leads to elevated head twitch behavior, indicative of a hallucinogenic effect. However, 24 hours post-injection, males display a rebound anxiety-like phenotype ($p=0.025$) while DOI-injected females exhibit no difference in behavior from saline-injected controls. In vivo 2-photon single cell calcium imaging reveals DOI-induced

modulation of PFC activity with many neurons showing elevated activity immediately following injection. We looked to probe the causal mechanisms of this specific DOI-activated population in driving the anxiolytic phenotype. To tag PFC neurons activated by DOI, we used a light- and calcium-gated transcription factor system, scFLARE2. In response to coincident blue light and high intracellular calcium, scFLARE2 triggers the release of a non-native transcription factor (tTA), which can drive the expression of a tTA-dependent TRE-reporter gene. We injected scFLARE2 and TRE-bReaChES, an excitatory redshifted opsin, into the PFC and implanted a fiber optic canula above. Blue light delivery immediately following DOI injection allowed for tagging and subsequent expression of the opsin in DOI-activated cells. Optogenetic reactivation of these neurons 24 hours following DOI-injection resulted in a marked reduction in anxiety-like behaviors in both sexes (Males: n=7,7, p=0.001; Females: n=6,7, p=0.03) compared to saline injected controls without driving elevations in head twitch behavior. These findings demonstrate that direct re-activation of DOI-responsive cells in the PFC is sufficient to recapitulate the acute anxiolytic effects of psychedelics without reproducing a hallucinogenic effect. This work sheds light on the circuit mechanisms underlying the therapeutic effects of psychedelic drugs via functionally-specific modulation of prefrontal cortical neurons.

Disclosures: **S. Lin:** None. **J. Muir:** None. **I. Aarrestad:** None. **H.R. Daniels:** None. **J. Ma:** None. **L. Tian:** None. **D.E. Olson:** None. **C.K. Kim:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.04/VV12

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NSF-GRFP Fellow
Brain and Behavior Research Foundation Young Investigator Award #30238
Searle Scholars Program #SSP-2022-107

Title: In vivo proximity labeling of prefrontal cortex axonal projections using TurboID

Authors: *M. ANGUIANO[1,2,3,4], E. L. LEWIS[2,5], E. M. FENTON[2,6], M. ROBLES[2,4], J. L. WHISTLER[2,5], A. S. NORD[2,6], C. K. KIM[2,4];
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Abstract: Various neurodevelopmental and neuropsychiatric disorders have been associated with either a loss or imbalance of proteins that influence overall cellular function. Having access to the proteome, or the entire makeup of proteins expressed by a cell, can unlock a more direct approach to studying abnormal neural activity due to changes in protein expression. Proximity labeling tools, such as TurboID, have given us new access to tagging proteins in vivo and

subsequently identifying and quantifying thousands of proteins at a subcellular level. Here, we aimed to identify proteomic differences underlying the neural circuits that are involved in driving motivated behaviors. The prefrontal cortex (PFC) has various downstream projections that have been implicated in bi-directionally altering motivated behaviors. Here we used a membrane-bound TurboID to tag and identify the proteins in PFC cell bodies and long-range projections to compare the proteome of PFC axons in the medial shell of the nucleus accumbens (NAc) and the periaqueductal grey (PAG) in mice. We show that we can successfully detect biotinylated proteins tagged by a membrane-targeted TurboID expressed in PFC cell bodies (2-way ANOVA interaction, $p< 0.0001$, $n=10$ male mice). Interestingly, even though prior studies have required multiple days of repeated biotin injection or delivery, here we were able to label proteins after even only a single dose of biotin. Furthermore, we demonstrate that the membrane-bound TurboID can robustly traffick long distances to axons in the NAc and PAG, producing biotinylation signal even in these sparse compartments ($n=3$). We enriched the biotinylated proteins using streptavidin beads, and analyzed 3 biological replicates using data independent acquisition proteomics at the UC Davis Proteomics Core (TimsTOF Pro 2; using Spectronaut). Our data shows enrichment of membrane and axon-related proteins (including those previously reported using single-cell RNA sequencing data), confirming the specificity of this tool in vivo. Finally, we also demonstrate that we can significantly tag and enrich proteins in the PFC of mice treated with a single dose of biotin and cocaine ($n=3$), highlighting the potential capabilities of using TurboID as an activity-linked proximity-labeling tool in vivo. This study provides a more direct approach at studying proteomic differences between frontal cortex projections and establishes an opportunity for finding future therapeutic targets.

Disclosures: **M. Anguiano:** None. **E.L. Lewis:** None. **E.M. Fenton:** None. **M. Robles:** None. **J.L. Whistler:** None. **A.S. Nord:** None. **C.K. Kim:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.05/VV13

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1R01EB024261
Lore McGovern
Lisa Yang
HHMI
NIH 1R01MH123403
NIH R01MH124606
John Doerr
CRUK

Title: Joint targeted in situ sequencing and immunostaining in thick, physically magnified brain tissue

Authors: *A. SINHA[1,2,3], D. GHOSH[2], H. SU[7,8], B. PRYOR[2], P. YIN[7,8], E. BOYDEN[2,9,4,5,6]; [2]McGovern Inst. for Brain Res., [3]Program in Hlth. Sci. and Technol., [4]Dept. of Biol. Engin., [5]Media Arts and Sci., [6]Dept. of Brain and Cognitive Sci., [1]MIT, Cambridge, MA; [7]Dept. of Systems Biol., Harvard Med. Sch., Boston, MA; [8]Wyss Inst. for Biologically Inspired Engin., Harvard Univ., Boston, MA; [9]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Mapping the precise identities and locations of RNAs and proteins in their native context is essential to understanding the diverse biological processes that occur in the brain. Together, the transcriptome and proteome help define cell types and states, and help maintain homeostasis, perform neural computations, and contribute to disease states.
Current methods primarily focus either on multiplexed RNA imaging, with 1-2 protein targets, or on multiplexed protein imaging. To date, no methods have yet been developed that enable multiplexed RNA and protein imaging in the same thick tissue specimen with high-resolution morphological features, enabling the assignment of transcripts to subcellular compartments within cells, and probing the relationship between RNA expression and protein expression at the nanoscale.
We report the ability to perform multiplexed immunostaining alongside targeted RNA *in situ* sequencing in thick intact brain tissue sections with nanoscale resolution. Our approach integrates targeted expansion sequencing (targeted ExSeq), with immunostaining with signal amplification by exchange reaction (immuno-SABER). We first immunostain for our protein targets of interest with DNA-barcoded antibodies, use a small molecule linker to covalently anchor RNA and proteins to the expansion gel, and hybridize gel-anchorable concatemers to the DNA barcodes. We then perform expansion microscopy by synthesizing a swellable gel within the specimen, expanding, and preparing a targeted *in situ* sequencing library for transcripts of interest. We then image the protein and RNA signals by performing iterative hybridization of fluorophore-labeled oligonucleotide probes and *in situ* sequencing, respectively. We demonstrate the utility of our technology by imaging RNA-defined cell type markers alongside cellular morphology markers and synaptic proteins in mouse cortex.

Disclosures: **A. Sinha:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US10995361B2. **D. Ghosh:** None. **H. Su:** None. **B. Pryor:** None. **P. Yin:** None. **E. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US10995361B2, Expansion Technologies.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.06/VV14

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Searle Scholars Program #SSP-2022-107
Burrows Wellcome Fund Career Award #1019469

Title: A proximity labeling tool for interrogating the intracellular milieu of the dopamine type 1 receptor

Authors: *C. J. DOUGHERTY[1,2,3], R. ZHANG[1,2,3], C. K. KIM[4,3];
[1]Univ. Of California Davis Neurosci. Grad. Program, Davis, CA; [2]Biomed. Engin. Grad. Group, [3]Dept. of Neurol., Univ. of California, Davis, Davis, CA; [4]Ctr. for Neurosci., Univ. of California, Davis, DAVIS, CA

Abstract: Dopamine signaling is mediated by dopamine receptors, members of the G protein-coupled receptor (GPCR) superfamily. GPCRs are known to initiate or modulate signaling by a variety of mechanisms, such as recruiting arrestin, associating with several kinds of G proteins, or forming heterodimers with other GPCRs. Ligands for the dopamine type 1 receptor (DRD1) can be classified according to their ability to bias certain pathways over others, a phenomenon known as biased agonism. Two factors determine the ligand-receptor system's pathway bias: (1) the conformational change induced in the receptor by a ligand and (2) the composition of the molecular environment and the distribution of proteins within the cell. Structure-guided approaches and protein-engineered tools have been developed to investigate (1), but few robust tools exist to investigate (2). To meet this need, we engineered a novel proximity labeling tool, dubbed DopPLer (**Dop**amine **P**roximity **L**abel**er**), capable of tagging only those proteins recruited to the activated DRD1. The tool consists of a DRD1 fused to a fragment of the engineered biotin ligase, TurboID, and β-arrestin2 fused to a complementary fragment. Upon activation, DRD1 recruits β-arrestin2, reconstituting TurboID, which then biotinylates nearby proteins. We confirmed our constructs via sequencing and screened them in HEK293T cells. Cell cultures were co-transfected with the constructs, stimulated with biotin and dopamine, and compared with cultures exposed to control conditions lacking dopamine, biotin, or both. Cultures where then fixed and stained with streptavidin and antibodies for epitope tags in the constructs. Biotinylation and protein expression were then captured using an automated imager and quantified using a cell segmentation algorithm. The streptavidin signal was significantly greater in wells treated with dopamine and biotin than in those treated with biotin alone (unpaired t-test with Welch's correction, $p = <0.0001$, $n = 12$ FOVs per condition), indicating dopamine activates DopPLer. Further characterization revealed DopPLer's pharmacological specificity resembles that of the native DRD1, as it produced a response intermediate to that to dopamine and that to control conditions when treated with DRD1-selective partial agonists (Dunnett's multiple comparisons test on 1-way ANOVA, $p = <0.0001$ for both comparisons, $n = 12$ FOVs per condition) and failed to produce a response significantly above that to control conditions when treated with a DRD2 agonist ($p = 0.3783$). We conclude from our results that DopPLer could prove a robust, agonist-dependent proximity labeling tool for interrogating DRD1's intracellular milieu.

Disclosures: C.J. Dougherty: None. **R. Zhang:** None. **C.K. Kim:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.07/Web Only

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Lisa Yang
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NIH R01MH122971
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NIH 1R01DA045549
John Doerr
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NIH R01NS130361
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NIH K99EB027706
R01DA045549

Title: In vivo optical clearing of mammalian brain

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[1]Brain and Cognitive Sci., [2]MIT Media Lab. and McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]Baylor Col. of Med., Houston, TX; [4]Biol., Westlake Univ., Hangzhou, China; [5]Mechanical Engin., Univ. of Minnesota, Minneapolis, MN; [6]HHMI, Cambridge, MA

Abstract: Methods for imaging structure and dynamics in the living mammalian brain are key to studies in practically every field within neuroscience. To date, such methods have taken tissue optical properties as given, and worked around them through physical or computational means; we here report that the optical properties of the living mammalian brain can themselves be changed. By using a small amount (e.g. ~1.5mM-40mM) of a carefully chosen biocompatible material to raise the refractive index of standard solutions employed for in vivo brain imaging, we could, on average, more than double the signal above background from the deepest cells visible at baseline, and visualize many cells that were originally too dim to see. This improvement was observed for both one-photon and two-photon imaging, at the depth limit for each technology, and for multiple fluorescent markers and sensors with emission wavelengths ranging from green to NIR. Visual tuning properties of neurons in the awake mouse cortex, during visual stimulation, as well as electrophysiological properties of neurons, assessed in vitro and ex vivo, were not significantly altered by the clearing agent. This methodology is complementary to, and can augment the performance of, physical and computational strategies for overcoming the light scattering of living brain tissue.

Disclosures: G. Talei Franzesi: None. **I. Gupta:** None. **M. Hu:** None. **K. Piatkevich:** None. **M. Yildirim:** None. **H. Andaraarachchi:** None. **J. Greenhagen:** None. **Z. Li:** None. **U. Kortshagen:** None. **M. Sur:** None. **E.S. Boyden:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.08/VV15

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Alana Foundation
Tom Stocky
NIH 1R01EB024261
Kathleen Octavio
Lore McGovern
Good Ventures
Lisa Yang
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HHMI
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ERC Synergy Program
NIH R01MH124606
John Doerr
NIH 1R01MH123977

Title: Expansion microscopy at subzero temperatures for ultrastructural preservation

Authors: *Y. LIU[1], C. ZHANG[2], T. SHIN[2], E. BOYDEN[2,3];
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Abstract: Expansion microscopy (ExM) is a powerful technique that enables nanoscale imaging on a conventional light microscope by physically expanding biological specimens permeated by a hydrogel (Science, 347(6221), 543-548). The ExM workflow involves a series of processes, including fixation, anchoring, gelation, softening, and expansion. In previous versions of ExM, gelation was performed at temperatures above zero, which we hypothesized could result in imperfect ultrastructural preservation. In this study, we present a novel approach called subzero expansion microscopy (subExM), which allows ExM to be conducted at subzero temperatures (-20°C or lower) prior to the softening step. This minimizes perturbations to cellular ultrastructures, and serves as a physical fixative without inducing excess protein-protein crosslinking that can mask epitopes and affect ultrastructure during expansion. To achieve this, we first employed a chemical that serves a dual purpose by both fixing the specimen, and enabling direct linkage of biomolecules to the gel matrix. This integration of fixation and anchoring into a single step simplifies the experimental workflow and minimizes disturbances to the specimen's ultrastructure. Subsequently, gelation is performed at subzero temperatures, allowing biomolecules to be bound to the gel matrix while maximally preserving protein information with minimal protein-protein crosslinking. We demonstrated the effectiveness of subExM by imaging various biological structures, including microtubules, mitochondria,

endoplasmic reticulum, and Golgi apparatus. We found that the ultrastructure of microtubules was better preserved and was more continuous compared to microtubules fixed using other methods. Antigens of these organelles were better preserved, exhibiting higher signal intensity and compatibility with post-expansion staining. We anticipate that subExM may broadly allow for the study of the architecture of biological systems with very high detail and fidelity.

Disclosures: **Y. Liu:** None. **C. Zhang:** None. **T. Shin:** None. **E. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Expansion Technologies, Massachusetts Institute of Technology.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.09/VV16

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: T32 MH112507
U19NS1237190
BWF CASI 1019469

Title: In vivo 2p imaging of excitatory synapses within interconnected brain regions using novel sensor split-iGluSnFR

Authors: *J. CHANDRA[1,2,3], B. LYU[5], Y. JIN[1,4], R. LIANG[4], G. YU[5], L. TIAN[4], C. K. KIM[2,3]; [1]Univ. Of California Davis Neurosci. Grad. Program, Davis, CA; [2]Ctr. for Neurosci., [3]Dept. of Neurol., [4]Dept. of Biochem. and Mol. Med., Univ. of California at Davis, Davis, CA; [5]Bradley Dept. of Electrical and Computer Engin., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA

Abstract: Glutamate is the one of the most ubiquitous neurotransmitters in the nervous system. As the main excitatory signaling molecule present at synapses, its signaling properties play a crucial role in regulating most neural circuits and behaviors. To record glutamate dynamics, glutamate-binding fluorescent sensors have been previously developed, most notably the iGluSnFR family. However, one limitation of this tool is that it non-specifically detects glutamate release arriving from any pre-synaptic input, making it impossible to record glutamate signaling at a genetically-specified synapse. The Tian lab recently developed a new sensor called split-iGluSnFR, which separates iGluSnFR into two inactive halves. When the two halves are expressed at either the pre- or post-synaptic terminal, respectively, they reconstitute in a synapse-specific manner and form a functional fluorescent glutamate sensor. Here we took advantage of cre-dependent viral strategies to express the pre-synaptic half of iGluSnFR in the primary motor cortex, and the post-synaptic half of iGluSnFR in the dorsal striatum. We implanted a Gradient Index Lens (GRIN Lens) in the dorsal striatum to enable optical access to the reconstituted sensor expressed deep in the brain. Using two-photon laser scanning microscopy, we were able

to image glutamate release specifically at these genetically- and anatomically-defined synapses (n=3 mice). We recorded glutamate dynamics both during spontaneous wakefulness, and also in response to repeated appetitive or aversive stimuli, highlighting the potential utility of this tool for tracking synapse-specific glutamate dynamics *in vivo* during behavior.

Disclosures: **J. Chandra:** None. **B. Lyu:** None. **Y. Jin:** None. **R. Liang:** None. **G. Yu:** None. **L. Tian:** None. **C.K. Kim:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.10/VV17

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Lisa Yang
HHMI
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NIH 1R01MH123977
NIH R01DA029639
NIH R01MH122971
NIH R01NS113499
NIH RF1NS113287
NSF 1848029
NIH 1R01MH114031
John Doerr
R01EY028219
R01MH126351
F32EY032756
F31EY033649

Title: Spatial multiplexing of fluorescent reporters for in vivo imaging in the visual cortex

Authors: *N. SHMOEL DAVID[1,2,3,4], K. R. JENKS[3], K. TSIMRING[3], C. LINGHU[6], M. SUR[3], R. DESIMONE[2], E. BOYDEN[2,3,4,5];
[2]McGovern Inst. for Brain Res., [3]Brain and Cognitive Sci., [4]Biol. Engin., [5]Howard Hughes Med. Inst., [1]MIT, Cambridge, MA; [6]Dept. of Cell and Developmental Biol. and Michigan Neurosci. Inst., Univ. of Michigan, Michigan, MI

Abstract: Molecular signaling is crucial for normal physiological processes, as it enables cells to convert inputs into outputs through intricate intracellular molecular networks. In addition, dysregulation of these signaling pathways is implicated in various diseases. Understanding these signaling networks requires mapping the intricate signal transduction networks both between and within cells in living organisms. Bioengineers have utilized fluorescent indicators of different

colors to study relationships between various signals within living cells for many years. However, multiplexing of different reporters is limited by the number of colors distinguished on a conventional microscope. Recently, we put forth a novel approach, which allows for more signals to be monitored than what is currently feasible with traditional multicolor imaging. By localizing distinct fluorescent reporters at stable but random locations throughout a cell, one can simultaneously monitor multiple signals (even of the same color) within a single living cell (spatially multiplexed imaging (SMI)). To implement SMI, we developed self-assembling peptide strategies to cluster reporters at stable but random points throughout a single cell, which we call signaling reporter islands (SiRIs). SiRIs were initially demonstrated in vitro, and recently we have been adapting SiRIs for in vivo use in the awake mouse brain. We expressed SiRI indicators for Ca2+ and PKA in layer 2/3 neurons of the visual cortex, and imaged the sensors' activities using two-photon microscopy. We found that SiRIs are stable within neurons and respond to visual stimuli, which allows for accurate analysis of how specific neuronal patterns engage these signaling pathways. In addition, we have now successfully co-expressed SiRIs for Ca^{2+} and PKA in the same neuron, enabling both signals to be monitored in single neurons of a living mouse brain. By utilizing this approach, we can use SiRIs to visualize signaling dynamics in response to visual stimuli and pharmacological cues.

Disclosures: **N. Shmoel David:** None. **K.R. Jenks:** None. **K. Tsimring:** None. **C. Linghu:** None. **M. Sur:** None. **R. Desimone:** None. **E. Boyden:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.11/VV18

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 1RF1MH132570-01

Title: Phosphorylation of pyruvate dehydrogenase marks the inhibition of in vivo neuronal activity

Authors: D. YANG[1], Y. WANG[2,1], ***T. QI**[2,1], X. ZHANG[1], L. SHEN[2,1], J. MA[2,1,3], Z. PANG[2,1], N. LAL[1], D. MCCLATCHY[1], K. WANG[1], Y. XIE[2,1], F. POLLI[1], A. MAXIMOV[1], V. AUGUSTINE[1,3], H. CLINE[1], J. YATES, III[1], L. YE[1];
[1]Scripps Res. Inst., La Jolla, CA; [2]The Scripps Res. Inst. - Grad. Program, La Jolla, CA; [3]UC San Diego, La Jolla, CA

Abstract: Linking behaviors and neural activity in the brain has been a central aim in neuroscience. For the past decades, immediate early genes (IEGs) such as c-fos has been widely used as molecular markers to search for neuronal activation across the brain. However, markers for the decrease of neuronal activity (i.e., inhibition) have been notably absent, hindering the comprehensive understanding of the brain function. In the current study, we established a novel

in vitro optogenetic-based biochemical screen, allowing precise control of neuronal activities with single action potential accuracy. Unbiased phosphoproteomic profiling revealed phosphorylated pyruvate dehydrogenase (pPDH) as a target for low neuronal activity. We then demonstrated that the level of pPDH inversely and dynamically correlated with the frequency of firing in primary neurons. In in vivo mouse models, immunohistochemistry labeling of pPDH detected neuronal inhibition across the brain induced by a wide variety of factors, spanning from artificial chemogenetic inhibition to natural stimuli including general anesthesia, sensory experiences, and natural behaviors. Furthermore, pPDH can be used in combination with cell-type markers and IEGs to study the bi-directional activity dynamics in molecularly defined neuronal populations. Thus, as an in vivo marker for neuronal inhibition, pPDH can serve as a potent tool to identify novel neural circuits for behavioral neuroscience.

Disclosures: **D. Yang:** None. **Y. Wang:** None. **T. Qi:** None. **X. Zhang:** None. **L. Shen:** None. **J. Ma:** None. **Z. Pang:** None. **N. Lal:** None. **D. McClatchy:** None. **K. Wang:** None. **Y. Xie:** None. **F. Polli:** None. **A. Maximov:** None. **V. Augustine:** None. **H. Cline:** None. **J. Yates:** None. **L. Ye:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.12/VV19

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NSF SBIR #2033921

Title: Self-assembled monolayer surface chemistry-conjugated ligands as a novel standardized method for interrogating astrocyte and neuron behavior and morphology.

Authors: E. G. THOMPSON[1], ***P. J. CALHOUN**[3], M. C. ROBITAILLE[4], J. A. CHRISTODOULIDES[4], J. M. BYERS[4], J. D. ROTHSTEIN[2], M. P. RAPHAEL[4]; [1]Neurol., [2]Johns Hopkins Univ., Johns Hopkins Univ., Baltimore, MD; [3]Nanocrine, Inc., Frederick, MD; [4]Materials Sci. and Technol. Div., Naval Res. Lab., D.C., DC

Abstract: Ligand availability is known to impact cell behavior, morphology, adhesion, intracellular signaling, and cell-cell coupling. Surface ligand availability, and it's measured activity, is underappreciated during *in vitro* assays with highly variable coating methods and assumptions leading to unaligned protocols and ambiguous results. To address this, we have developed a standardized surface utilizing self-assembled monolayer surface chemistry to conjugate cyclized Arg-Gly-Asp (cRGD) ligands at known densities and derived mean spacing in parallel with a gold sensor chip to enable measurements of cRGD ligand activity. This approach enables tuning of ligand availability which we show affects cell morphology and behavior. Furthermore, we have demonstrated this technology is uniquely capable of phenotypically differentiating cellular insults such as viral infection. Finally, we carried out a

direct comparison study between our substrates (Nanocrine Surface Chemistry Biochips), Matrigel, poly-D-lysine, and poly-D-lysine plus laminin, to define key benefits when used with primary human astrocytes, primary mouse astrocytes, and primary mouse neurons.

Disclosures: E.G. Thompson: None. **P.J. Calhoun:** A. Employment/Salary (full or part-time):; Nanocrine, Inc.. **M.C. Robitaille:** None. **J.A. Christodoulides:** 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.; Nanocrine, Inc. **J.M. Byers:** 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.; Nanocrine, Inc.. **J.D. Rothstein:** None. **M.P. Raphael:** 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.; Nanocrine, Inc..

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.13/VV20

Topic: I.04. Physiological Methods

Support: R01DA05320001A1

Title: A genetically-encoded light-gated transcriptional reporter for detecting opioid peptides

Authors: *J. DING, W. WANG;
Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: A genetically-encoded light-gated transcriptional reporter for detecting opioid peptidesAuthors Jiahui Ding, Wenjing Wang**Abstract**Opioid receptors (ORs) and peptides are involved in critical physiological and pathological processes, such as pain regulation and reward in the brain. Monitoring opioid peptide release is essential to study the regulation of endogenous opioid signaling and their effects on pain modulation and reward. Bioanalytical sensors and real-time sensors provide insights into the dynamics of opioid peptide release. However, it is still not possible to gain genetic access to the subsets of neurons regulated by opioid peptides during specific behaviors for further characterization by sequencing and reactivation. Integrator sensors, Specific Protein Association tools giving transcriptional Readout with rapid Kinetics (SPARK), can convert the protein-protein interactions (PPI) to fluorescent signals and leave permanent, quantifiable marks for further manipulation. It has been successfully applied to monitor dopamine receptor D1 (DRD1) and β2-adrenergic receptor (β2AR) activation by detecting the interaction between arrestin (a downstream signaling factor) and DRD1/B2AR. I will show the design and optimization of SPARK for detecting opioid peptides based on opioid receptors. The

improved opioid-SPARK will provide genetic access to the neuronal populations regulated by endogenous opioid peptides.

Disclosures: J. Ding: None. **W. Wang:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.14/VV21

Topic: I.04. Physiological Methods

Support: University of Michigan

Title: Engineering genetically encoded integration sensors for whole-brain mapping of G_q-protein-coupled receptor ligands

Authors: *A. A. SOTO ACEVEDO, W. WANG;
Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: G-protein-coupled receptors (GPCRs) compose the largest superfamily of membrane proteins in the human genome and account for approximately one-third of available FDA-approved drugs, making them invaluable targets in drug development due to their extensive roles in physiological processes. G_q-protein-coupled receptors (G_qPCRs), a subset of GPCRs, play an important role in immunity, making it critical to study their neuronal signaling. However, a limited number of tools allow the detection of endogenous GPCR ligands. To address this issue, our group developed a genetically encoded sensor, M-SPOTIT2, for detecting opioid agonists for opioid receptors (ORs) at the cellular level, generating a persistent green, fluorescent mark upon OR activation. This design consists of a protein single-chain with an OR, circularly permuted green fluorescent protein (cpGFP), and the $G_{\alpha i}$-mimic nanobody, Nb39. In the basal state, Nb39 binds to cpGFP and prevents its maturation, leading to no fluorescence. Upon agonist activation, Nb39 binds to the OR, allowing the fluorophore to mature, resulting in an integrated green, fluorescent signal. This research focuses on adapting this sensor for G_qPCRs via directed evolution methods. Ultimately, this new sensor will allow whole-brain mapping of endogenous G_qPCR ligands, such as histamine, acetylcholine, and serotonin, *in vivo*.

Disclosures: A.A. Soto Acevedo: None. **W. Wang:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

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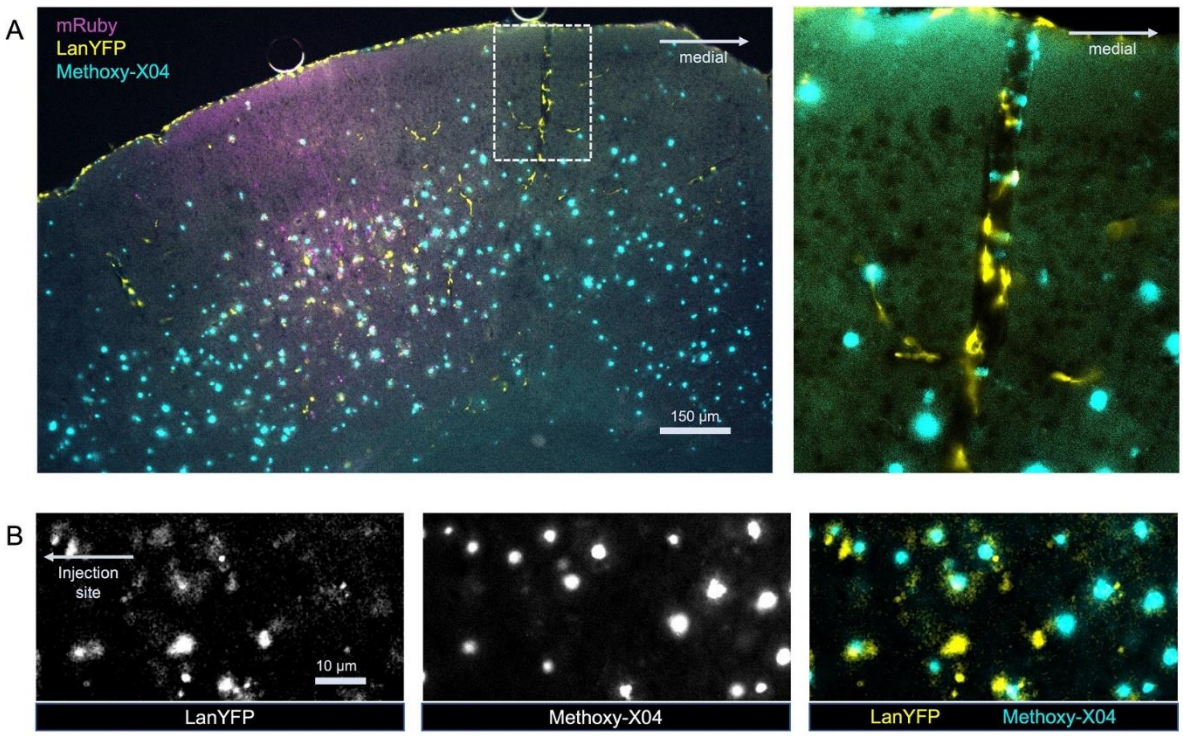
Topic: I.04. Physiological Methods

Support: NIH Grant 5R21EB024694
NIH Grant 5R21EY033085
Cornell Mong Fellowship

Title: A novel inducible genetically encoded secreted tracer (iGEST) for modeling protein transport and accumulation in Alzheimer's Disease.

Authors: *C. S. BRUNKHORST, C. G. KERR, C.-Y. EOM, C. B. SCHAFFER, N. NISHIMURA;
Meinig Sch. of Biomed. Engin., Cornell Univ., Ithaca, NY

Abstract: Understanding protein transport and accumulation is essential for developing countermeasures for neurodegenerative diseases like Alzheimer's (AD). Prior studies have relied upon tracking injected dyes or labeled proteins, such as amyloid beta (Aβ). Direct injections do not recapitulate the physiology of Aβ, which is produced and secreted locally by cells. We developed an inducible, genetically-encoded secreted tracer (iGEST) consisting of a fluorescent protein (LanYFP) fused to a secretion tag (rat follicle stimulating hormone beta (FSHb)), which mimics the secretion of endogenous proteins into the extracellular space. Microinjection of adeno-associated virus (AAV) to drive expression of the iGESTs provides spatial control and an inducible promoter (doxycycline-dependent TET-Off system) enables temporal control of expression. Doxycycline was introduced into the mouse diet seven days prior to viral injections. A mix of AAV2/9 for the TET-Off activator with a neural promoter (hSyn-tTA), iGEST (TRE-FSHb-LanYFP), a non-secreted red fluorescent protein (hSyn-mRuby2) (50 nL, 3:25:10 respectively) was injected into the cortex of adult AD (5xFAD) and wild type controls (n=2). After 21 days, doxycycline was stopped to initiate iGEST production and secretion. After another 21 days of active iGEST secretion, mice were perfused, and brains sectioned for histological analysis. iGESTs are expressed and secreted in a small group of neurons at the injection site in cortex of the right hemisphere (yellow, FigA) in the same region as the non-secreted label (magenta). iGESTs accumulated in vessels near the injection site. Interestingly, in AD animals, iGESTs appeared on some vessels with cerebral amyloid angiopathy (CAA) visualized with methoxy-X04 (cyan, FigA) with some overlapping regions of CAA and iGEST. iGEST accumulated along the cortical surface near the injection site, the central sagittal sinus and interhemispheric fissure. Finally, we observed some colocalization of iGEST and Aβ plaques near, but not distant to the injection site (FigB).



Disclosures: **C.S. Brunkhorst:** None. **C.G. Kerr:** None. **C. Eom:** None. **C.B. Schaffer:** None. **N. Nishimura:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.16/VV23

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant DP1MH119428
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DGIST R&D Program of the Ministry of Science and Information and Communications Technology (ICT) 22-PCOE-01
JSPS Overseas Research Fellowships 60-236

Title: Tagging active neurons during specific timing in behavior

Authors: *K. NAGAHAMA[1,4], J. HYUN[9,4], H. NAMKUNG[2], N. L. MIGNOCCHI[10], S.-E. ROH[3], P. D. HANNAN[11], S. KRÜSSEL[3], C. KWAK[3], A. MCELORY[3], B. LIU[3], D. LEE[12], R. L. HUGANIR[3], P. F. WORLEY[3], A. SAWA[3,5,6,7,13], H.-B. KWON[3,8,10];
[1]Neurosci., Johns Hopkins Univ. Sch. of Med., BALTIMORE, MD; [2]Psychiatry, [3]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Neurosci., [5]Psychiatry, [6]Genet. Med., [7]Pharmacol., [8]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [9]DGIST, Daegu Gyeongbuk Inst. of Sci. and Technol., Daegu, Korea, Republic of; [11]Max Planck Florida Inst., [10]Max Planck Florida Inst., Jupiter, FL; [12]Anat., Korea Univ. Col. of Med., Seoul, Korea, Republic of; [13]Mental Hlth., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD

Abstract: Identification of responsible neuronal populations is essential to understand causal relationship between neural activity and behavior. However, the previous immediate early gene (IEG)-based tagging system has a limitation in the temporal resolution because it requires several hours to express reporter genes in neurons. To overcome this limitation and identify more precise causality between active neurons and specific behaviors, we previously developed a calcium (Ca2+)-and light-gated switch system named as Cal-Light. Cal-Light expresses reporter genes in neurons when Ca2+ influx happens coupled with blue light shining, which presents labeling and modulation of behavior at high spatiotemporal resolution. Although Cal-Light was demonstrated to be useful for tagging and manipulating neuronal activities during the behavior, it still has some limitations such as light sensitivity and non-specific tagging. Here, we newly updated Cal-Light as soma-targeted Cal-Light (ST-Cal-Light) to expand the application of the Cal-Light. By fusing the transmembrane domain of kainite receptor 2 (KA2), ST-Cal-Light construct was localized in cell soma to increase sensitivity to action potential-induced Ca2+ influx in the soma on *in vitro* conditions. We confirmed the improvement of light sensitivity compared to the original-Cal-Light (OG-Cal-Light) in cultural conditions. We then applied the ST-Cal-Light to lever-press behavior, fear learning, social interaction test, and kainic acid (KA)-induced seizure experiment and successfully label and manipulate the responsible neuronal populations in each behavioral task. To target specific cell types relevant to behavior, we developed a conditional ST-Cal-Light knock-in (ST-Cal-Light-KI) mouse line, which express the ST-Cal-Light in cre recombinase-dependent manner. We crossed the ST-Cal-Light KI mice with two different cre-expressing mouse lines (Emx-Cre, PV-Cre) and confirmed significant efficiency and specificity of the tagging on each neuronal cell type. We also developed a Cre-dependent-expressed version of the ST-Cal-Light to target specific cell types in diverse Cre-mouse lines. As suggested in tons of our evaluation, the ST-Cal-Light has a potential to facilitate understanding of causality between activity and behavior at higher spatiotemporal resolution.

Disclosures: K. Nagahama: None. **J. Hyun:** None. **H. Namkung:** None. **N.L. Mignocchi:** None. **S. Roh:** None. **P.D. Hannan:** None. **S. Krüssel:** None. **C. Kwak:** None. **A. McElory:** None. **B. Liu:** None. **D. Lee:** None. **R.L. Huganir:** None. **P.F. Worley:** None. **A. Sawa:** None. **H. Kwon:** None.

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

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Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.17/VV24

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: W. M. Keck Award KF-05617242

Title: Tracking expression of AAV cargos in living animals with bioluminescence: timing of light generation, signal attenuation by tissue and luminescence generated from defined neuron types

Authors: *C. CALLICOATTE, M. METCALFE, A. LUPTAK, J. PRESCHER, O. STEWARD;
Anat. and Neurobio., Univ. of California Irvine, Irvine, CA

Abstract: AAVs are being used increasingly to express therapeutic cargos for neurological disorders. A bottleneck in developing AAV-based expression paradigms is that assessment of cargo expression currently requires post-mortem assays such as qPCR, immunocytochemistry, or in situ hybridization. To overcome that, we are developing platforms and paradigms to track AAV cargo expression in living animals with bioluminescent reporters. Bioluminescence generated by the action of the enzyme luciferase on its substrate luciferin offers advantages because light can be detected in living mice by *in vivo* imaging. Here, we define parameters of bioluminescence from AAV-driven expression of firefly luciferase (AAV-fLuc) following injections into the brain of adult mice. To define timing and persistence of expression, mice received intra-cortical injections of AAV-fLuc and luminescence was assessed using the In Vivo Imaging System (IVIS). Luminescence induced by luciferin ramped up over the first 2 days and persisted with repeated injections without decrement for 36 days. To define timing of light emission, mice were imaged at 10-minute intervals after luciferin injection. Luminescence peaked 40 minutes after injection and then declined to 50% of peak by 40 minutes. To define attenuation of signal by skull and skin, mice received luciferin, were imaged, and then brains were rapidly dissected and imaged by IVIS. Luminescence generated from dissected brains averaged 492% of what was seen in the living mouse just before brain dissection, indicating approximately 65% signal attenuation by skull, skin, and fur. Remarkably, luminescence persisted in freshly dissected brains for many minutes, decreasing to 50% of initial values by 15 minutes. Intracortical injections of AAV-fLuc transduce neurons and glia non-selectively. To assess luminescence generated from a single neuron type (pyramidal neurons in layer V that give rise to the corticospinal tract-CST), we used an intersectional genetic approach. Mice received intra-spinal cord injections of AAVrg-Cre, which is retrogradely transported to the cells of origin of the CST. Mice then received intra-cortical injections of AAV expressing Cre-dependent fLuc. With this paradigm, only the layer V neurons transduced to express Cre will express fLuc. Luciferin injections induced robust luminescence at the site of the cortical injection that ramped up to a peak over 6 days, allowing quantitative assessment of luminescence generated by a single population of cortical neurons in their native tissue environment. These results define parameters and conditions for future studies tracking AAV-driven expression of therapeutic cargos.

Disclosures: **C. Callicoatte:** None. **M. Metcalfe:** None. **A. Luptak:** None. **J. Prescher:** None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder, scientific advisor, and has economic interests in the company Axonis Inc, which is developing novel therapies for spinal cord injury and other neurological disorders..

Poster

PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.18/VV25

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Development of a novel highly sensitive oxytocin ELISA

Authors: *S. SUGINO, M. KOJIMA, F. AKUTSU, T. NISHIBU;
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Abstract: Oxytocin is a peptide hormone comprising nine amino acids. It is produced in the hypothalamus and released mainly from the posterior pituitary gland following childbirth and during lactation. As well as promoting uterine contraction and milk production, it also has stress-relieving, anxiolytic, and fear-reducing effects and plays a role in the development of maternal behavior. Due to these properties, oxytocin is often referred to as the "happy hormone" or "love hormone". Recently, oxytocin has attracted attention in the treatment of mental disorders such as depression and autism and in the development of functional food materials. We investigated several commercially available oxytocin ELISA kits, but the existing kits require a large volume of sample and complicated pretreatment using a C18 column and organic solvent. Consequently, we embarked on developing a novel ELISA for oxytocin that only needed a small sample and simple pretreatment. First, we constructed an oxytocin competition ELISA, which has much higher sensitivity (LOD: 1.25 pg/mL) than the commercial kit, by using oxytocin antibody, biotin-label oxytocin, streptavidin conjugated HRP, and a chemiluminescent substrate. It has been reported that oxytocin binds proteins and other molecules in the sample and these can affect measurement by inhibiting oxytocin and antibody interaction. We accordingly investigated various methods for removing the measurement inhibitor in the sample and found a novel pretreatment method for adding acid and gel to the sample and centrifuge. In conventional methods, the required sample volume is 250-1,000 μL and the pretreatment time is from two hours to overnight. However, with our method, measurement with a 50 μL sample can be completed in 30 minutes by a simple manipulation.This ELISA showed good recoveries (89.3-98.5%) in spike recovery tests in human plasma, serum, urine and saliva. Our method is superior to the conventional method (46.2-108%) and non-pretreatment method (167-374%). In addition, in the dilution linearity test with human plasma, serum, urine, saliva mouse/rat plasma, and serum, all samples showed good linearity ($R > 0.97$). Next, oxytocin in saliva collected from 11 healthy subjects was measured by ELISA, and the oxytocin level was detected in 10 out of 11

samples.In conclusion, our novel ELISA is expected to be a useful tool in basic research on oxytocin using human subjects, mice, rats, and other animals.

Disclosures: **S. Sugino:** A. Employment/Salary (full or part-time):; FUJIFILM Wako Pure Chemical Corporation. **M. Kojima:** A. Employment/Salary (full or part-time):; FUJIFILM Wako Pure Chemical Corporation. **F. Akutsu:** A. Employment/Salary (full or part-time):; FUJIFILM Wako Pure Chemical Corporation. **T. Nishibu:** A. Employment/Salary (full or part-time):; FUJIFILM Wako Pure Chemical Corporation.

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PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.19/VV26

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant AG071978
NIH Grant AG073887
NIH Grant CA255979
NIH Grant GM148812

Title: Labeling and analysis of phagocytic clearance by express FRET probes

Authors: *V. DIDENKO[1,2], C. MINCHEW[1,2];
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Abstract: We describe a FRET-basedtechnology detecting active phagocytic cells in live cell cultures andsuspensions, such as cultured non-adherent cells, phagocytic cell cultures, orcultured brain tumor cells. The spectrofluorimetric method relies on stabilized1B topomers, working as FRET probes, which selectively react with5′-hydroxylated flush-ended DNA. This end configuration is exclusively producedduring lysosomal digestion of phagocytosed DNA and is a specific marker ofphagocytic DNA digestion. Using cultured phagocytic J774A cells andglioblastoma cell cultures, we demonstrate that the approach can labeldifferent cell types participating in phagocytosis, with the lower detectionlimit of ~ 20active phagocytes in a standard cell culture sample.By assessing phagocyticreactions occurring in co-cultures of brain tumor cells and macrophages, theapproach can be useful in studies of immune system responses to tumors.

Disclosures: **V. Didenko:** None. **C. Minchew:** None.

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PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.20/VV27

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Multidimensional characterization of mouse brain S-palmitoylation by a novel biochemical method

Authors: *A. SEKIYA[1], A. FUJISAWA[2], T. KATO[2], M. YAMAMOTO[1];
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Abstract: Protein *S*-palmitoylation, also called *S*-acylation, is a covalent addition of palmitate to a specific cysteine residue on proteins and is reversibly regulated by palmitoylation and de-palmitoylation enzymes. This post-translational modification plays various roles in protein functions, especially protein translocation to membranes. A wide range of proteins, including synaptic proteins, are identified as *S*-palmitoylated proteins. Postsynaptic marker PSD-95 is a well-known *S*-palmitoylated protein and *S*-palmitoylation of PSD95 is essential for its postsynaptic localization. Although *S*-palmitoylation controls various cellular functions, analytic methods are highly limited due to their complicated, time/labor-consuming procedures and highly non-specific backgrounds. In this study, we developed a novel, versatile, easy, rapid, and specific method to assess the protein *S*-palmitoylation, called **Rapid** **S**ubstitution of **P**rotein *S*-**A**cy**L**ation for **M**ultifunctional-tag (^{RapidS}PALM). ^{RapidS}PALM is based on a stepwise chemical conversion of *S*-acyl group on proteins to our original multifunctional-tag (MfTag) within only 3 hours. Due to three features of MfTag, 1) yellow fluorophore, 2) affinity tag, and 3) high molecular weight (~5 kDa) backbone, ^{RapidS}PALM enables us to perform five types of assay, A) quantification of total *S*-palmitoylation level, B) visualization of *S*-palmitoylated proteins in SDS-PAGE gel, C) comprehensive isolation of *S*-palmitoylated proteins, D) estimation of a number of *S*-palmitoyl on the target protein, and E) determination of stoichiometry of *S*-palm/non-palm form of the target proteins. To validate utility of ^{RapidS}PALM, we applied ^{RapidS}PALM to neuronal samples. At first, we quantified the total *S*-palmitoylation level in various mouse tissues and revealed brain shows the highest *S*-palmitoylation. In subcellular fractioned samples from adult mouse brain, most *S*-palmitoylated proteins accumulated in the postsynaptic fraction. Next, we tried to isolate MfTag-labeled proteins converted by the ^{RapidS}PALM and successfully detected the typical *S*-palmitoylated proteins including PSD-95, with very low non-specific backgrounds. Furthermore, ^{RapidS}PALM allowed to estimate numbers of palmitoyl-group on 7 proteins and to determine the stoichiometry of PSD-95 in brain. Finally, we tried to investigate effects of stimuli on *S*-palmitoylation levels in cultured mouse neuroblastoma and revealed that nitric oxide dramatically reduced *S*-palmitoylation level. These results suggest ^{RapidS}PALM has a large potential for both proteomic and individual analysis under time-saving and low-background conditions.

Disclosures: **A. Sekiya:** A. Employment/Salary (full or part-time):; Funakoshi Co., Ltd. **A. Fujisawa:** A. Employment/Salary (full or part-time):; BioDynamics Laboratory Inc. **T. Kato:** A. Employment/Salary (full or part-time):; BioDynamics Laboratory Inc. **M. Yamamoto:** A. Employment/Salary (full or part-time):; Funakoshi Co., Ltd..

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PSTR115. Biochemical and Molecular Tools for Neuronal Tagging

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR115.21/VV28

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: EU Grant NSC Reconstruct / GP 100-28

Title: Maximizing spatial biology - A workflow combining 3D imaging with 2D multiparameter analysis of adult mouse brain

Authors: K. BIGOTT, S. RAHMATI, L. PRISCO, S. MERZ, G. EBEL, *A. BOSIO, M. JUNGBLUT;
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Abstract: Spatial biology is an emergingfield that studies spatial organization of cells and molecules within tissuesto decipher complex biological processes. Current methods for two dimensionalimmunofluorescent microscopy only provide information from tissue sections,whereas three dimensional analysis utilizes immunophenotyping of intact organs,but only addresses a restricted set of markers. To maximize spatial analysis,we developed a workflow to combine 3D and 2D imaging. 3D analysis is firstapplied for visualization of a selected set of markers at single cellresolution in the whole organ. Subsequently, target structures within thesample are selected and sectioned for multi-parameter 2D analysis with hundredsof markers. For 3D imaging we developed amatching set of components including a light-sheet fluorescence microscope(UltraMicroscope Blaze™), a non-toxic organic solvent based clearing method(MACS® Clearing Kit) and recombinant REAfinityTM antibodies coupled to brightand stable Vio® dyes. For 2D analysis we applied ourMACSima™ Imaging Cyclic Staining (MICS) procedure for cyclic immunofluorescentmicroscopy. This technology enables the analysis of tissue samples withhundreds of antibody-fluorochrome conjugates on a single section at single-cellresolution. Sections are imaged in a cyclic process that includes fluorescentstaining with antibody-fluorochrome conjugates, image acquisition and erasureof the fluorescence signal.Mouse brain hemispheres werefixed, permeabilized, stained with fluorescent antibody conjugates againstNeurofilament and Parvalbumin, dehydrated and rendered transparent byrefractive index matching. With the full 3D view, we selected the cerebellum asa target region and prepared tissue sections accordingly, a process termedlight sheet guided histology. After rehydration, sections of the target regionwere prepared and subjected to MICS. Results revealed that fluorochromeconjugates used for 3D staining were still detectable after sectioning,allowing for back-registration of the target region. Successful neural markerdetection (e.g. GFAP, MBP, NeuN, ß-tubulin III, VGLUT1) in MICS demonstratedepitope stability during the entire process of sample preparation and allowed phenotypingof divers neural subpopulations.Insummary, this workflow provides the link between two imaging technologies. Theability to obtain both, a comprehensive whole organ context and detailedinformation about cellular diversity in a spatial context from a single samplemakes the procedure a valuable tool in spatial biology to maximize ourunderstanding of the cellular and molecular architecture in whole organs.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.01/VV29

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant R21NS121589

Title: Single-cell rnaseq profiling of peripheral blood mononuclear cells reveals distinct transcriptomic signatures in moyamoya disease

Authors: *Z. DEMIRAG[1], H. UCHINO[1], K. TOKAIRIN[1], S. RAO[1], T. CHIANG[1], A. G. LEE[2], M. Y. CHENG[1], G. K. STEINBERG[1];
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Abstract: Background: Moyamoya Disease (MMD) is a complex cerebrovascular disease characterized by progressive narrowing of cerebral arteries, which can lead to severe outcomes such as stroke. Studies have reported dysregulation in extracellular matrix-related genes and elevated circulating inflammatory cytokines/chemokines in MMD, suggesting a role of immune responses in the development of MMD. In this study, we employed single-cell RNA sequencing (scRNA-seq) to investigate the cellular dand the transcriptomic landscape of circulating immune cells in MMD.
Methods: Whole blood samples were collected from bilateral MMD patients (n=3), non-MMD patients (n=2, aneurysm or cavernous malformation) and healthy controls (n=2). Peripheral blood mononuclear cells (PBMCs) were isolated and cryopreserved. ScRNA-seq libraries were constructed using Chromium Single Cell 3' Gene Expression v3 Library and sequencing was performed on NovaSeq6000 (PE150). ScRNA-seq data were demultiplexed and mapped using the Cell Ranger package (10X Genomics), followed by downstream preprocessing and analysis. Differently expressed genes (DEGs) were identified and Ingenuity Pathway Analysis (IPA) was used to elucidate top biological functions and pathways in each cell type.
Results: Preliminary analysis showed proportional differences in certain cell types between MMD and healthy controls, including CD8+ NKT, Naïve CD8+ T, CD4+ NKT, Naïve B cells and non-classical monocytes. DEGs for CD8+ NKT, Naïve CD8+ T and CD4+ NKT highlighted in MMD were further analyzed: Disease and biological function analysis showed predicted activation in cell death and inhibition in cell viability, cell movement, proliferation and migration. Pathway analysis revealed predicted activation in eIF2 (eukaryotic initiation factor-2) in all three cell types, most prominently in CD8+ NKT cells. In addition, pathway analysis showed

predicted inhibition in natural killer cell signaling and autophagy pathways.
Conclusion: We have profiled the transcriptomic landscape of circulating immune cells in MMD and highlighted the involvement of CD8+ NKT cells, Naïve CD8+ T cells and CD4+ NKT cells. These cell types exhibit pathways involved in cellular stress, including inhibiton of natural killer cell signaling and disruption in autophagy, which can lead to compromised cytotoxic functions. Ongoing studies include validation of key cell types and genes in an expanded cohort of patient samples. Our findings shed light on the intricate immune responses implicated in MMD, offering valuable insights into potential contributions to the disease's pathophysiology.

Disclosures: Z. Demirag: None. **H. Uchino:** None. **K. Tokairin:** None. **S. Rao:** None. **T. Chiang:** None. **A.G. Lee:** None. **M.Y. Cheng:** None. **G.K. Steinberg:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.02/VV30

Topic: I.02. Systems Biology and Bioinformatics

Title: Whole genome-based DNA methylation profiling in COVID-19 patients reveals alterations in pathways linked to neurological dysfunctions

Authors: *S. ZAMEER[1], J. GORDEVICIUS[3], E. ANIS[1], Q. SHA[1], M. L. GALVIS[1], J. A. STEINER[1], M. X. HENDERSON[1], A. POSPISILIK[2], P. BRUNDIN[4], L. BRUNDIN[2]; [1]Dept. of Neurodegenerative Sci., [2]Dept. of Metabolism and Nutr. Program, Van Andel Inst., Grand Rapids, MI; [3]Vugene LLC, Vilnius, Lithuania; [4]Roche, Basel, Switzerland

Abstract: Abstract The sever acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a highly transmissible viruswhich causes a life-threatening illness called coronavirus (COVID-19). It has cost millions ofdeath worldwide. This novel RNA betacorona virus is manifested by varying clinical symptomsranging from asymptomatic to mild to severe systemic illness with deadly outcomes. Muchevidence revealed the differences in the severity of COVID-19 infection varied widely accordingto host factors and comorbidities. It is critical to understand the interplay of genetic and epigeneticfactors and host response to this fatal virus. A substantial number of epigenome-wide associationstudies acknowledged that SARS-CoV-2 manipulate the host epigenome via DNA methylation andalter the host antivirus defense mechanisms and immune systems related to interleukin, helper T-cell differentiation and leucocyte activation. Moreover, infections after SARS-CoV-2 exposure ledto post-acute sequelae, which involve a wide array of neurological abnormalities, such as mentalhealth, extrapyramidal, movement, and cognition disorders. There is a need to investigate thechanges in whole genome of COVID-19 patients responsible for these underlying neurologicalabnormalities. In this regard, we explored for the first time key epigenetic changes using wholegenome-based DNA methylation profiling, in COVID-19 positive patients with different diseaseseverities and COVID-19 negative controls. We found significant hypomethylation in enhancerregion of the entire genome spanning 1-5kb in

COVID-19 patients with mild, moderate, and severesymptoms and it becomes more pronounce as the severity of infection increases. Furthermore, thegene set enrichment analysis revealed that the COVID-19 infection is associated withneuroinflammation, mood and developmental disorders and downregulation of neurondevelopment, neuron projection morphogenesis and glutaminergic signaling. Our results provideevidence of reduced DNA methylation across the entire genome as a key factor for neurologicaldysfunctions in COVID-19 patients.Key words: COVID-19, DNA methylation, epigenome, neuroinflammation

Disclosures: **S. Zameer:** None. **J. Gordevicius:** None. **E. Anis:** None. **Q. Sha:** None. **M.L. Galvis:** None. **J.A. Steiner:** None. **M.X. Henderson:** None. **A. Pospisilik:** None. **P. Brundin:** None. **L. Brundin:** None.

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PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR116.03/VV31

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH grant U01MH122592

Title: High-resolution mapping of cell type-specific DNA (hydroxy)methylation in the human brain during postnatal development and aging

Authors: *J. CHIEN[1], J. LI[2], R. VADUKAPURAM[3], A. KOZLENKOV[3], S. DRACHEVA[4,3], E. A. MUKAMEL[2];
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Abstract: Methylation of genomic cytosine is a critical epigenetic modification that helps to define the identity of diverse neuron types. Methylcytosine accumulates in neurons during postnatal development, including at CA and CT dinucleotides. A subset of methylated cytosines (mC) undergoes further conversion to hydroxymethylcytosine (hmC). mC and hmC have distinct cell type specific distributions throughout the genome, and both epigenetic marks have complex correlations with RNA expression. While extensive studies have focused on transcriptome and methylome changes during development, few have specifically distinguished the dynamic regulation of mC and hmC, especially in human brain neurons.
We measured the genome-wide dynamics of cell type specific DNA (hydroxy)methylation and their relationship with transcriptome during development and aging in human neurons. We profiled (hydroxy)methylation and gene expression in two major neuronal subtypes-GABAergic(GABA) and glutamatergic(GLU)-in human prefrontal cortex from 99 donors. Our findings reveal that cell type and age together account for a substantial portion of inter-individual variance in DNA methylation. We observe the gradual conversion of mC into hmC throughout the lifespan, with this change being more prominent in GLU neurons compared to GABA

neurons.
We identified a greater number of differentially expressed (DE) genes across developmental stages in GLU neurons compared to GABA neurons, with the majority of DE genes showing significant changes during infancy (0-1 year old). While mCG was negatively correlated with RNA expression for most genes, we found a positive correlation between hmC and RNA expression. However, we also identified a subset of genes that exhibit opposite relationships. This suggests the influence of epigenomic modifications other than DNA methylation on the expression of genes during postnatal development.
In summary, our study provides valuable information about the cell type-specific dynamics of DNA (hydroxy)methylation during development and its association with transcriptomic changes, thus providing insights into the regulatory mechanisms underlying neural maturation and plasticity.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR116.04/VV32

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant R01NS120746

Title: Genome wide 5mC and 5hmC patterns determine unique transcriptional signatures, transcriptional regulators and alternative splicing of neural cell types in mouse brain

Authors: *X. WEI[1,2], J. LI[1,3], Z. CHENG[4], S. WEI[4], G. YU[4], M. L. OLSEN[5];
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Abstract: The DNA modifications, 5-methylcytosine (5mc) and 5-hydroxymethylcytosine (5hmc), represent powerful epigenetic regulators of temporal and spatial gene expression across unique CNS cell types in healthy brain development, adult brain and in the context of learning and memory. Aberrant global and cell type specific DNA methylation patterns are observed in neuropsychiatric, neurodevelopmental and neurodegenerative disease. Yet, how the cooperation of these genome wide epigenetic marks vary across different neural cell populations serve to determine unique transcriptional signatures and alternative splicing has not been evaluated. Here we applied Nanopore sequencing to obtain a complete, genome wide, single base resolution atlas of 5mc and 5hmc modifications in neurons, astrocytes and microglia in the young adult mouse

cortex (over 40 million CpG sites). Cell type specific RNA sequencing was performed in tandem to evaluate the transcript expression of all coding genes. Our analysis revealed the number of 5mC methylated CpG sites across the three cell types was similar, but surprisingly the number 5hmC methylated CpG was significantly enriched in astrocytes relative to the other two cell populations. By integrating the DNA methylation status with coding gene expression level obtained from RNA sequencing of each cell population, we confirmed previous reports indicating 5mC methylation in the promoter region is associated with gene repression. Our analysis also revealed the level 5hmC in the promoter region positively correlates with gene expression. Further, we identified novel transcription the cooperate with 5mC and 5hmC methylation to regulate exon inclusion. Finally, we provide this base resolution DNA methylation data as an interactive online resource (**NAM-ME**, Neuronal, Astrocyte, Microglia Methylation) for those interested in the methylome landscape in health and disease.

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PSTR116. Genomics, Proteomics and Bioinformatic Approaches

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Program #/Poster #: PSTR116.05/VV33

Topic: I.02. Systems Biology and Bioinformatics

Support: 1UM1MH130981
UF1MH128339

Title: Robust suite of tools for prioritizing and visualizing single cell ATAC sequencing peaks

Authors: *S. SOMASUNDARAM, N. JOHANSEN, A. OSTER, M. WIRTHLIN, M. HOOPER, E. THOMAS, Z. YAO, B. TASIC, T. L. DAIGLE, Y. BEN-SIMON, J. K. MICH, B. LEVI, J. T. TING, T. BAKKEN, J. MILLER, E. LEIN;
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Abstract: Assay of Transposase Accessible Chromatin (ATAC) sequencing is a popular method for determining chromatin accessibility across the genome. ATAC-seq reveals regions on the chromosomes that bind transcription factors or other DNA binding elements, and these regions often correspond to enhancer elements that control the expression of genes. Single cell ATAC (scATAC) sequencing can be applied to reveal the cell type-specific gene regulatory landscape that distinguishes cell types from each other. Recent work has shown that cell type-selective enhancers can be applied in Adeno-associated virus (AAV) vectors to drive gene expression selectively in the same cell types that showed chromatin accessibility. However, the process of enhancer discovery is not efficient. Several comprehensive suites of analysis tools have been developed for scATAC sequencing analysis from alignment of single cells to clustering to identifying enriched regions (or “peaks”) of aligned reads for each cell type. Downstream

software like DiffBind can quantify differential peak binding across cell types and yet hundreds to thousands of peaks can be selected and these tools fall short for prioritizing and selecting the optimal peaks for experimental testing and application.
To bridge this gap, we present a robust suite of software tools in the R programming language for ranking, visualizing, and exploring cell type-specific enhancers and their properties. *PeakRankR* takes a series of predefined peaks for multiple cell types and prioritizes the best differential peaks for experimental validation using just a few important peak features. *SeqFindR* aids to build synthetic peaks by deconstructing the sequence grammar of enhancers for each cell type. It can identify and highlight the Transcription Factor Binding Sites (TFBS) or core elements, both known and novel, in a peak sequence. *Sorting and Visualizing Enhancers (SAVE)* provides a shiny-based table browser interface for retrieving, filtering, sorting, and visualizing the prioritized peaks in different cell types. Together, this set of tools can help in selecting and experimentally testing optimum peaks faster for translational research across species. We have validated and scored enhancers to benchmark the open suite of peak selection tools that can be found in the Peakverse GitHub repository (https://github.com/AllenInstitute/Peakverse).

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PSTR116. Genomics, Proteomics and Bioinformatic Approaches

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Program #/Poster #: PSTR116.06/VV34

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant UM1MH130981-01

Title: Implementing cell type taxonomy and ontology standards for BICAN and beyond

Authors: *J. A. MILLER[1], D. OSUMI-SUTHERLAND[2], L. NG[1], N. JOHANSEN[1], H. KIR[2], S. Z. K. TAN[2], Y. ZHANG[3], P. L. RAY[1], Z. YAO[1], H. ZENG[1], R. H. SCHEUERMANN[3], M. J. HAWRYLYCZ[1], E. S. LEIN[1];
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Abstract: The advancement of single-cell transcriptomic and epigenomic technologies has led to an explosion of cell type classifications across multiple organs and organisms. In BICAN alone, several efforts are underway for characterizing brain cell types in development and adulthood using a variety of experimental protocols and complementary study designs. The Human and Mammalian Brain Atlas (HMBA) focuses on creating a cross-species, multi-omics atlas of the

adult brain at high anatomic resolution. With approximately 5,000 distinct cell types in identified in adult mouse brain alone, along with the additional complexity expected from cross-study and cross-species comparisons, it will be essential to have standards and tools for tracking cell types within a study, to integrate historical knowledge of related cell types, and to facilitate cross-study comparison. Here we present a set of taxonomy and ontology standards under development as part of the HMBA, but that could be of broad use for other cell type classification efforts in BICAN, HuBMAP, and HCA. First, we present a taxonomy standard (the 'common cell type nomenclature') which extends the typical cell type classification workflow by providing a standard format for storing cell type nomenclatures, annotations, relationships, anatomic location, and functional properties, along with interactive tools for its application. Second, we extend a community ontology of cell types (the 'Cell Ontology') to include cell types in primary motor cortex spanning multiple mammalian species, as a starting point for defining data-driven cell type ontologies from whole organ systems. This ontology includes reliable molecular marker genes for each cell type derived using NS-Forest. Third, we introduce a system of permanent URLs (PURLs) for sharing versioned taxonomies both pre- and post-publication, and which provide direct integration between taxonomies and associated ontologies. Finally, we present initial efforts at applying these tools to publicly accessible cell type classifications in whole mouse and whole human brain to demonstrate their utility. Together these standards and tools fill an important gap in current cell type classification studies, and we expect them to evolve for improved usability and to capture additional user requests.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant 1U24MH130918-01

Title: A community tool for mapping cell type labels onto arbitrary transcriptomic data sets

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Abstract: Allen Institute studies have aimed to establish a transcriptomics-based “parts list” for the mouse brain by collecting single cell RNA sequencing data from millions of cells distributed throughout the whole brain and using complex non-linear statistical modeling to group these cells into clusters with common gene expression patterns (e.g. Tasic et al. 2018, Yao et al. 2023). Most recently, Yao et al. devised a whole mouse brain cell type taxonomy composed of more than 5,000 discrete transcriptomic cell types that show spatial localization in companion MERFISH data. This work, and related mouse and human brain cell type taxonomies, represents a major scientific advance and a valuable resource to the neuroscience community. Here, we introduce the Allen Community Data Mapping (CDM) portal, which enables users to map arbitrary gene expression profiles collected by other labs onto reference mouse or human cell type taxonomies and label transfer cell type classifications from the reference onto the query data set. The CDM portal is implemented in a cloud-based architecture built with Amazon Web Services such that neuroscientists anywhere can upload and map their data, regardless of coding experience or local compute resources. CDM’s modular design allows any algorithm that relies on common inputs and outputs to be implemented for mapping. We initially include three mapping algorithms, ranging in complexity from simple Pearson’s correlation to mapping in an auto-encoder’s latent space. All algorithms return probabilistic cell type assignments for the unlabeled data. Similarly, we present three reference taxonomies as a starting point: mouse whole brain, human whole brain, and a higher-resolution look at a single human cortical area. The CDM portal gives highly consistent results in reasonable time. Testing on data from this latter Seattle Alzheimer’s Disease Brain Cell Atlas (SEA-AD) reference yields 80% agreement between algorithms at the lowest of two cell type taxonomy levels and 98% at the highest level. Testing on a whole mouse brain MERFISH data set of 550 genes finds that the costliest algorithms can map 4 million cells in just under 2 hours. We provide this tool as a service to the community as part of Allen Brain Map (brain-map.org) in the hopes that all groups studying brain cell types can speak a common language as we further refine our understanding of what cell types are, how they function, and how they change with aging and disease. This work is supported by National Institute of Mental Health award number 1U24MH130918-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.08/VV36

Topic: I.02. Systems Biology and Bioinformatics

Support: NIMH R24 MH114788
NIDA UM1 DA052244

Title: Neuroscience Multi-Omic (NeMO) Archive and Analytics: BRAIN Initiative Resources for Neurogenomic Data Submission, Access, and Analysis

Authors: *A. MAHURKAR[1], S. ADKINS[1], S. AMENT[2], R. CARTER[2], A. CHATTERJEE[2], J. CRABTREE[1], V. FELIX[1], M. GIGLIO[1], B. HERB[4], T. HODGES[1], K. IFEONU[1], S. NADENDLA[1], D. OLLEY[2], J. P. RECEVEUR[3], M. SCHOR[2], A. WATANABE[2], O. WHITE[2]; [1]Inst. for Genome Sci., [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Univ. of Maryland Sch. of Med., Baltimoer, MD; [4]Univ. of Maryland Baltimore, Baltimore, MD

Abstract: The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative promotes the development and application of technologies to describe the temporal and spatial dynamics of cell types and neural circuits in the brain. The wealth, depth and quality of multi-omic data generated through the BRAIN Initiative is unprecedented. It includes bulk and single cell RNA-seq and epigenomic data from developing and adult brains across multiple species, as well as multi-modal datasets that integrate these omic data with spatial information, neuronal morphology, and neurophysiology. In addition, the Single Cell Opioid Response in the Context of HIV (SCORCH) project is generating omics data from brains of individuals with HIV and with and without substance use disorders. To promote smooth access to omics-based brain data from diverse sources, we developed the Neuroscience Multi-Omic Archive (NeMO Archive; www.nemoarchive.org), a data repository that is specifically focused on the storage and dissemination of omic data from the BRAIN Initiative, SCORCH, and related brain research projects. Currently, NeMO includes over 400 terabytes of multi-omic sequence and derived analysis data represented in over 1.2 million individual files generated through two major BRAIN Initiative efforts, the BRAIN Initiative Cell Census Network (BICCN), and the BRAIN Initiative Cell Atlas Network (BICAN). The NeMO Archive makes data access easy through a web-based portal that allows users to filter based on numerous metadata fields and download data. Additionally, users can use APIs to search and access the data at NeMO. The information at the NeMO Archive will, in part, enable understanding of cell types in the mammalian brain and of cell states associated with development and eventually disease. It will also provide the basic knowledge to guide the development and execution of predictive and machine learning algorithms in the future.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

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Topic: I.02. Systems Biology and Bioinformatics

Support: R01EY011261 to HTC
R01EY027437 to HTC
P41GM103533 JRY
R01MH067880 JRY

Title: A pipeline for efficient cell-type specific metabolic labeling to enhance LC-MS/MS detection of the newly synthesized proteome relevant to neuronal plasticity

Authors: *R. WANG, Y. XIE, D. MCCLATCHY, Y. MA, J. YATES, III, H. CLINE;
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Abstract: The investigation of newly synthesized proteins (NSPs) is a key aspects in our understanding of brain plasticity. To study NSPs in a cell-type specific context, our lab has established a pipeline where we use mMetRS^{KI} mouse lines to metabolically label NSPs with a non-canonical amino acid azidonorleucine (ANL), and directly detect biotinylated peptides (DiDBiT) with LC-MS/MS. However, for those who want to apply this technique in their study, the first challenge is to identify the optimal ANL treatment regime that maximizes NSP labeling and proteome coverage in their cell types of interest, without losing the necessary temporal precision. Obtaining optimally labeled sample is nontrivial and has great impact on quantification and statistics in later steps. To provide guidance on designing labeling regime, here we share our data on: 1) ANL pharmacokinetics in brain tissue within 24 hours following one ANL i.p. injection. 2) ANL-NSP labeling within 24 hours following one ANL i.p. injection as well as multi-day multi-injection. 3) NSP labeling efficiency in different cell-type specific promotor-driven mMetRS^{KI} mice. 4) NSP labeling efficiency in mMetRS^{KI} heterozygous and homozygous mice. 5) Genotyping strategies to detect and exclude germline recombination when breeding homozygous mMetRS^{KI} mice. 6) NSP labeling efficiency in different brain regions. 7) NSP labeling efficiency in cortical neurons across different ages. 8) Optimal SDS concentration compatible with click chemistry. Our data not only offer comprehensive comparisons across a broad spectrum of conditions, but also illustrate the application potential of this method for a variety of scientific inquiries, with differing focuses on cell type, temporal scale, brain region and age. Our results thus serve as a guidance future application.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.10/VV38

Topic: I.02. Systems Biology and Bioinformatics

Support: Supported by Olink Proteomics

Title: Exploratory Analysis of 3000 Proteins in Postmortem Human Brain Tissue Lysates Using Proximity Extension Assay

Authors: *A.-L. LIND, C. CAMBRONERO, R. LAMERS, M. FONTES, T. AWAD;
Olink Proteomics, Uppsala, Sweden

Abstract: The development of early precise diagnostics and effective management strategies of neurological disorders is challenging, in part because of the complexity and inaccessibility of the affected systems and tissues. There is a great unmet need, and potential, for novel tools to accelerate the advancement of modern neurology precision medicine. Diagnosis and management of neurological disorders typically relies on clinical evaluations, imaging analysis, and cerebrospinal fluid tests of a limited number of biomarkers. Multi-omic analyses of bio-banked precious postmortem donor brain tissues offer a unique window into disease mechanisms and accelerate the identification of novel drug targets. Leveraging recent technological advances in sample-sparing scalable proteomic methods, such as the Proximity Extension Assay (PEA), can accelerate insights into pathophysiological mechanisms and the identification of novel drug targets. Biomarkers identified in broad biomarker screens can be further validated and used to enable early disease detection and patient stratification, and monitor disease progression and treatment responses. In this exploratory technical study, we examined, for the first time, the detectability of 3,000 human proteins in 15 postmortem human brain tissue lysate samples using PEA technology. The study protocol and platform performance were evaluated for data quality and technical reproducibility. The results showed robust detectability for the neat dilution of this complex sample matrix for the majority of assays, including hundreds of proteins relevant for neurological conditions. Thus, we conclude that the PEA proteomic platform can serve as a valuable tool for neurological studies involving brain tissues.

Disclosures: **A. Lind:** A. Employment/Salary (full or part-time):; Olink Proteomics. **C. Cambronero:** A. Employment/Salary (full or part-time):; Olink Proteomics. **R. Lamers:** A. Employment/Salary (full or part-time):; Olink Proteomics. **M. Fontes:** A. Employment/Salary (full or part-time):; Olink Proteomics. **T. Awad:** A. Employment/Salary (full or part-time):; Olink Proteomics.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Grant OAC1920103
NSF Grant DGE2139757

Title: Biological Patterns Revealed through Intersectional Analysis of Genomic Splicing and Protein Folding

Authors: *K. D. BOWDEN[1], I. R. SINHA[2,3], J. P. LING[3];
[1]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [2]Neurosci., [3]Pathology, Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Splicing of pre-mRNA is an important cellular process that causes the inclusion or exclusion of specific exons and results in proteomic diversity across cell types. AlphaFold is a recent protein structure prediction which uses an open source AI to predict protein structures from an amino acid sequence. ASCOT is a database which uses publicly available RNA-sequencing datasets to collect instances of splicing variants across the genome. Each of these splicing variants results in at least two different mRNA isoforms. These recent innovations give us the ability to generate novel protein structures more efficiently, allowing us to examine the impact alternative exon splicing has on protein conformation. In this study we show that splicing events, among other trends, predominantly affect alpha-helices within secondary protein structures. Previous large-scale studies of protein structure have not included the impact of alternative exon splicing. Our results add an important level of depth to understanding the consequences of exon splicing and cell-type specific proteins. This study demonstrates the ability of computational tools to reveal trends of biological relevance and specifically the influence of transcriptomic changes on protein conformation.

Disclosures: K.D. Bowden: None. **I.R. Sinha:** None. **J.P. Ling:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.12/VV40

Topic: I.02. Systems Biology and Bioinformatics

Support: U.S. Department of Energy, ASCR #KJ0403010
U.S. Department of Energy, ASCR #KJ0403020
National Science Foundation Graduate Research Fellowship
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Title: Protein design for neuroscience via multimodal and interpretable deep learning

Authors: *S. IBRAHEEM[1], M. A. WRIGHT[4], S. FARRELL[5], A. TRITT[6], H. GARCÍA MARTÍN[7,8,9,10], K. E. BOUCHARD[4,7,2,3];
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Abstract: Protein design has advanced neuroscience through new tools and methods such as neuroindicator proteins (e.g., XFPs, GCaMPs, etc.,) that have become central to brain imaging techniques. Advances in protein design would open up the possibility of designing neuroindicators that have, e.g., improved fluorescence properties and enhanced ability to target receptors of interest. However, standard methods for designing proteins use directed evolution to, for example, enhance a protein's fluorescence. This Edisonian approach is inefficient and costly. The development of more precise, targeted methods of protein design would facilitate the design of a new generation of molecular tools for understanding the brain.
Modern AI has the potential to greatly accelerate protein design. Recent work demonstrates AI's ability to predict protein structure and to design new protein sequences. However, while the function of a protein is determined by its 3D structure, most AI protein design focuses on 1D sequences. We hypothesized that an AI model jointly trained on protein sequence and structure data would outperform sequence-only models. The joint model would better be able to relate sequence, structure, and function within its latent space, which would improve the model's ability to design useful proteins. Towards this end, we trained a joint structure-sequence model, incorporating protein structure into a recent sequence-based protein design model. We trained this model on a stability dataset with more diverse proteins than its original dataset. We further utilized the recently developed Demixed PCA dimensionality reduction technique to explore the learned latent representations of the model.
We found that joint sequence-structure models were better able to generate novel protein sequences with enhanced stability than sequence-only models, supporting our hypothesis. In ongoing work, we are exploring the latent space of the models, examining whether the sequence-structure models have better structured, more traversable latent spaces. We will then apply this framework to the enhancement of other protein properties, such as fluorescence, creating a pipeline for the flexible design of neuroindicator proteins.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

Support: National Natural Science Foundation of China (81960454, 81960344, and 82260533)
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Guizhou Provincial Science and Technology Projects ([2020]1Z066)
Guizhou Provincial People's Hospital National Science Foundation (GPPH-NSFC-2019-18, 2019-09 and GPPH-NSFC-D-2019-17)

Title: Identification of Potential Biomarkers and Therapeutic Targets in Glioblastoma Using Machine Learning Algorithms

Authors: S. YANG[1], Z. KONG[2], M. DENG[2], J. LIU[2,1], **J. ZHANG**[2], *Y. TAN[2];
[1]Guizhou university, Guizhou, China; [2]Guizhou Provincial People's Hosp., Guizhou, China

Abstract: Objective: This study aimed to explore potential biomarkers and therapeutic targets in glioblastoma using machine learning algorithms applied to transcriptomic analysis. Methods: We obtained transcriptomic data from multiple glioblastoma cohorts. In the training set (TCGA-GBMLGG cohort), differentially expressed genes (DEGs) between glioblastoma and normal brain tissues were identified. Additionally, unsupervised clustering was performed to classify glioblastoma into two molecular subtypes, which exhibited significant differences in prognosis and tumor microenvironment. Subsequently, the Weighted Gene Co-expression Network Analysis (WGCNA) algorithm was employed to identify hub genes highly correlated with molecular subtyping. The intersection genes between DEGs and hub genes were used to construct a glioblastoma risk scoring model. We employed a total of 101 algorithms, including 10 commonly used machine learning algorithms, for model construction using the training set. The accuracy of the model was validated using the validation set (two CGGA cohorts and three GLIOVIS cohorts). Finally, the performance of the optimal model was tested on the test set (six GEO cohorts). Additionally, a pan-cancer analysis of IGFBP2 was conducted. Furthermore, the expression of model genes in glioblastoma and paired adjacent tissues was validated using qRT-PCR. Results: An immune and prognosis-related risk scoring model, termed Immune and Prognostic Score (IPS), was developed using an ensemble algorithm. IPS was found to be an independent risk factor for overall survival and progression-free survival in glioblastoma patients, surpassing the predictive accuracy of traditional clinical variables. IPS was also significantly associated with the immune microenvironment. High IPS scores were indicative of increased sensitivity to immunotherapy and variations in response to different chemotherapy drugs. The expression levels of seven feature genes, including IGFBP2, were validated and shown to align with bioinformatics results. Furthermore, IGFBP2 demonstrated elevated expression in tumors across various human cancers and exhibited close associations with prognosis, immune checkpoint genes, and RNA editing-related genes. Conclusion: The IPS model provides a predictive tool for assessing glioblastoma prognosis and guiding personalized treatment strategies. The identified feature genes, notably IGFBP2, hold potential as tumor biomarkers and therapeutic targets.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

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Guizhou Provincial Science and Technology Projects ([2020]1Z066)
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Title: Identifying subarachnoid hemorrhage macrophage-associated biomarkers based on integrating bulk and single-cell sequencing data by machine learning and deep learning

Authors: S. YANG[1], M. DENG[2], Z. KONG[2], J. LIU[2], Y. TAN[3], *J. ZHANG[4];
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Abstract: Background: Subarachnoid hemorrhage (SAH) is a severe condition characterized by bleeding in the brain's subarachnoid space. Timely and accurate SAH diagnosis is crucial for prompt intervention and improved patient outcomes. Our study aimed to identify key genes for enhancing diagnostic accuracy and guiding therapeutic interventions.
Methods: SAH rat models were established using endovascular puncture, and brain tissue samples from the right temporal cortex were subjected to single-cell and bulk RNA-seq, powerful high-throughput sequencing techniques. Meticulous analysis of the single-cell transcriptome data allowed us to identify distinct subpopulations of macrophages, including a unique subset specifically associated with SAH. Through the highly efficient hdWGCNA method, we identified 160 genes closely associated with SAH-associated macrophages. Rigorous statistical approaches, including univariate analysis and lasso regression, refined the gene selection to a final set of 10 robustly associated genes. Machine learning algorithms facilitated the construction of a diagnostic model using these genes and relevant clinical information. The model demonstrated exceptional diagnostic accuracy with an area under the curve (AUC) of 1.0 in both the training and validation datasets. Additionally, the MCPcounter algorithm estimated immune cell populations within SAH brain tissue, visualized through a heatmap. Furthermore, a convolutional neural network (CNN) model achieved a sensitivity and specificity of 1.0 in classifying SAH cases. Molecular docking techniques identified potential drugs targeting specific molecular mechanisms associated with SAH.
Results: The diagnostic model using the 10 selected genes exhibited outstanding performance, with an AUC of 1.0 in both the training and validation datasets. The heatmap integrating cell abundance and gene expression data provided valuable insights into the cellular composition of SAH. The CNN model demonstrated exceptional sensitivity and specificity, supporting its potential as a diagnostic tool. CD14, GPNMB, SPP1, and PRDX5 were prominently expressed in SAH-associated macrophages, offering potential therapeutic targets. Network pharmacology analysis identified potential drugs targeting these genes for SAH treatment.
Conclusion: Our study characterizes macrophage subpopulations, identifies key genes, and develops a robust diagnostic model for SAH. CD14, GPNMB, SPP1, and PRDX5 are potential therapeutic targets in SAH. Further research is needed to validate these findings and explore clinical implications, advancing our understanding and treatment of SAH.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR116.15/VV43

Topic: I.02. Systems Biology and Bioinformatics

Support: 2021ZD0200900
2022YFC340010
2018SHZDZX05
23S41900300

Title: Development of gene editing tools for gene therapy of neurosystem-related diseases

Authors: *Z. XU[1], S. CAI[2], Q. MA[2], N. GAO[2], H. ZHOU[2];
[1]Inst. of Neuroscience, Chinese Acad. of Sci., shanghai, China; [2]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China

Abstract: Introduction and objectives:CRISPR-Cas system, as a defense mechanism of bacteria against foreign nucleic acid invasion, especially the Class II CRISPR-Cas system, has been widely studied due to the advantage of its single effector protein. However, the research on the novel compact RNA-targeting CRISPR-Cas13 system is not extensive enough, and different CRISPR-Cas13 proteins have varying preferences (PFS) for targeting nucleic acids. The search for more compact and widely applicable new Cas13 proteins is beneficial for expanding the toolbox of gene editing and promoting the development of the pharmaceutical and health industries, especially in gene therapy for brain diseases.Methods:We used bioinformatics techniques to mine class II CRISPR-Cas13 system proteins from microbial genomes and metagenomes. We further validated and identified the candidate proteins' cleavage activity and cleavage preference characteristics using eukaryotic cell lines (293T cell line) and prokaryotic cells (Escherichia coli).Results:Through bioinformatics mining techniques, we identified several novel CRISPR-Cas13 proteins from microbial genomes and metagenomes. Among them, a new RNA-targeting CRISPR-Cas13 protein, designated as DZ78, exhibited the strongest RNA cleavage activity. Similar to previously reported Cas13 proteins, this protein also contains a conserved HEPN domain (RXXXXH), which not only cleaves exogenous RNA but also processes CRISPR-array precursors, releasing sg-DR form of sgRNA. Moreover, this protein has a significant sequence preference when targeting RNA, showing a preference for 5'-G. By targeting the exogenous gene mCherry fluorescent protein expressed in 293T cell line, we found that the optimal cleavage efficiency of this protein was achieved when the length of the targeting spacer was around 30 bp. In addition, under the guidance of sgRNA, this protein could effectively cleave endogenous gene expression products in eukaryotic cells (293T cell line).Conclusions:By constructing a bioinformatics mining pipeline, we discovered a relatively compact RNA-targeting novel VI CRISPR-Cas13 system (designated as DZ78) from nature. This protein can effectively cleave exogenous and endogenous RNA, and has potential

applications in gene therapy and research for neurodegenerative diseases. This discovery provides a new toolbox for the development of RNA-targeting gene editing tools.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.16/VV44

Topic: I.02. Systems Biology and Bioinformatics

Title: A multiomics and neuroimaging approach to identification and treatment of motor impairment

Authors: *A.-G. DENNIS;
Temerty Fac. of Medicine, Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada

Abstract: Many neurological conditions and neurodegenerative diseases that implicate cerebellar dysfunction involve gene mutations, while others are due to injury or environmental causes. This researcher previously studied task-based fMRI in healthy humans, found statistically significant differences in functional connectivity in sensorimotor cerebellar regions attributable to differences in handedness, and proposed a right-hand sensorimotor cerebellar model. Continuing from previous work, here the researcher proposes combining different omics approaches with neuroimaging data to further explore conditions affecting motor function. Using a range of techniques, data, and sources, this research provides perspectives on the early identification of disease states and patterns leading to potential therapeutics.

Disclosures: **A. Dennis:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.17/VV45

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R35GM138173

Title: Development of a PCA-based calibration model for quantifying DNA oligonucleotides analogous to microRNAs 219 and 132

Authors: *S. ENRIQUEZ, C. A. BAKER;
Dept. of Chem. and Biochem., New Mexico State Univ., Las Cruces, NM

Abstract: The suprachiasmatic nucleus of the hypothalamus (SCN) plays an important role in regulating 24-hour biological cycles, known as circadian rhythms. The processing of light to modulate a molecular circadian clock has a direct influence over various physiological processes. Of note, the expression of gene-regulating microRNAs (miRNA), such as miR219 and miR132, plays a role in entraining the central molecular circadian clock to the time of day. Interestingly, accumulation of miR219 and miR132 within the SCN and dysregulated circadian rhythms are both hallmarks of Alzheimer's disease (AD). We hypothesize a neuroendocrine role for these miRNAs which may contribute to the synchronizing of the molecular circadian clock distributed in tissues throughout the body. Quantifying miRNAs remains a challenge due to their small size (typ. 20-22 nucleobases). This challenge is further complicated by the small volume analyses required to observe signaling processes in living cells and tissues. Rolling circle amplification (RCA) is an isothermal technique well suited for miRNA amplification. While RCA is commonly applied to the detection of miRNAs as biomarkers, the potential for RCA as a straightforward quantitation assay is underexplored. Developing an RCA-based quantitative assay will allow us to characterize the dynamic release of these miRNAs from *ex vivo* SCN tissue and explore their potential as a pathway in the development of AD.
We have developed a multivariate calibration methodology for determining starting oligonucleotide concentration from observations of real-time fluorescence during RCA amplification of synthetic standard oligonucleotides. We identified 4 potential quantitative metrics that can be extracted from the real-time fluorescence curve and correlate well with starting oligonucleotide concentration. Further on, we combined all four quantitative metrics by principal component analysis (PCA) and derived a model which can serve as a predictor for initial concentration in RCA reactions. This model is effective at least to starting concentrations as low as 2 pM, although strict lower limits of detection by this method are still under investigation. The PCA model was developed using synthetic DNA oligos with sequences analogous to miRs 219 and 132, and specificity has been demonstrated via cross-reactivity controls for these sequences.
We have shown proof of concept for a PCA-based calibration model allowing effective quantitation of oligonucleotides at low pM concentration based on RCA. Work continues to adapt and characterize this calibration model for use with biologically derived miRNAs.

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Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

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Topic: I.01. Molecular, Biochemical, and Genetic Techniques

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Title: Identifying miRNA : mitochondrial transcript interactions using chimeric RNA sequencing

Authors: *E. EISS, M. K. MEFFERT;
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Abstract: MicroRNAs (miRNAs) are small noncoding RNA molecules that are loaded onto an Argonaute (Ago) protein to function as a guide for the RNA-induced silencing complex (RISC) to identify and regulate the expression of target mRNAs, most often through recruitment of deadenylation and RNA degradation enzymes. Accurately identifying the mRNA targets of miRNAs is essential to understanding their physiological impacts, but biological factors can confound the ability of bioinformatic target prediction software to accurately predict these interactions: these include non-canonical binding of the miRNA to target areas outside of the 3' untranslated regions (UTRs) of mRNAs, occlusion of expected interaction sites by RNA binding proteins or mRNA secondary structure, and differential localization of target RNAs and miRNAs. To circumvent the challenges of bioinformatic prediction, our lab has optimized an Argonaute crosslinking and immunoprecipitation (Ago-CLIP) technique, which we call CIMERAseq (crosslinking and immunoprecipitation followed by intermolecular ligation of endogenous RNAs within Argonaute followed by high-throughput sequencing). In this technique, miRNAs and their target RNAs are immobilized in-vivo by UV-crosslinking, trapping them within the Argonaute protein, which is then immunoprecipitated using anti-Ago2 antibodies. Key subsequent steps of intramolecular ligation serve to ligate the 3' end of the miRNA to the 5' end of its target, forming a chimeric RNA molecule that can be sequenced to reveal endogenous interactions in a semi-quantitative fashion. We performed CIMERAseq on mouse forebrain homogenate and discovered an unexpected preponderance of miRNA : mitochondrial RNA interactions in the detected chimeric sequenced RNAs. It is currently unknown how miRNA and/or Ago are able to enter mitochondria, although both RISC components are found in mitochondria. Diverse and opposing effects of mitochondrial RISC on mitochondrial gene expression have been reported, with both translation activation or translation inhibition observed in different contexts. Our ongoing research aims to address gaps in knowledge by furthering the understanding of miRNA : mitochondrial RNA targeting and downstream functional impacts.

Disclosures: E. Eiss: None. **M.K. Meffert:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.19/VV47

Topic: I.02. Systems Biology and Bioinformatics

Support: ZIAMH002881

Title: Mitochondria interactome in Parvalbumin Interneurons during Gamma Stimulation

Authors: *D. PANJA, R. TIAN, Z. LI;
Natl. Inst. of Mental Hlth., Natl. Inst. of Hlth., Bethesda, MD

Abstract: Parvalbumin interneurons in the central nervous system exhibit fast spiking activity and synchronize with other neurons in neural networks to play a vital role in controlling the brain rhythms underlying the organization and functioning of neural circuits involved in various cognitive processes, including perception, attention, memory, and information processing. Parvalbumin neurons modulate the activity of excitatory neurons and generate gamma oscillations to control the population activity of neurons. Their capacity to fire action potentials at high frequencies necessitates a high energy expenditure to maintain the essential ion gradients and restore membrane potentials. The mitochondria in parvalbumin neurons possess distinctive characteristics in terms of abundance and morphology. There have been some whole-cell proteomics studies of parvalbumin neurons but studies on mitochondrial protein interactomes of parvalbumin neurons have been limited. To explore the molecular mechanism that accommodates the high energy demand of these interneurons during gamma oscillations, we conducted sensory gamma entrainment in mito-tag mice expressing HA tags in parvalbumin neurons by exposing them to simultaneous visual and auditory stimulation at 40 Hz, followed by immuno-capture of mitochondria. The isolated mitochondria were subjected to LC-MS, and IDEP9 suite of bioinformatic software was used to examine the mitochondrial interactome. Over 2200 proteins were found to be increased in the mitochondria isolated from mice exposed to 40-Hz sensory stimuli. These proteins are associated with mitochondrial organization, mitochondrial respiratory chain complex assembly and transport, oxidative phosphorylation, endoplasmic reticular organization, mitochondrial gene expression, and glycoprotein and cellular lipid metabolic process. Of these 2200 proteins, only 24 (1%) do not belong to resident mitochondrial proteins, Golgi proteins, fatty acid binding proteins, RNA binding proteins, trafficking proteins, kinesis family, or dopamine and fatty acid metabolism proteins. This mitochondrial proteome associated with 40 Hz-stimulation provide a framework to generate hypotheses of how the structure and function of mitochondria in PV neurons are regulated to adapt to their unique physiological properties. Experimental testing of such hypotheses will inform the rational design of molecular interventions for brain disorders involving PV neurons.

Disclosures: D. Panja: None. **R. Tian:** None. **Z. Li:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

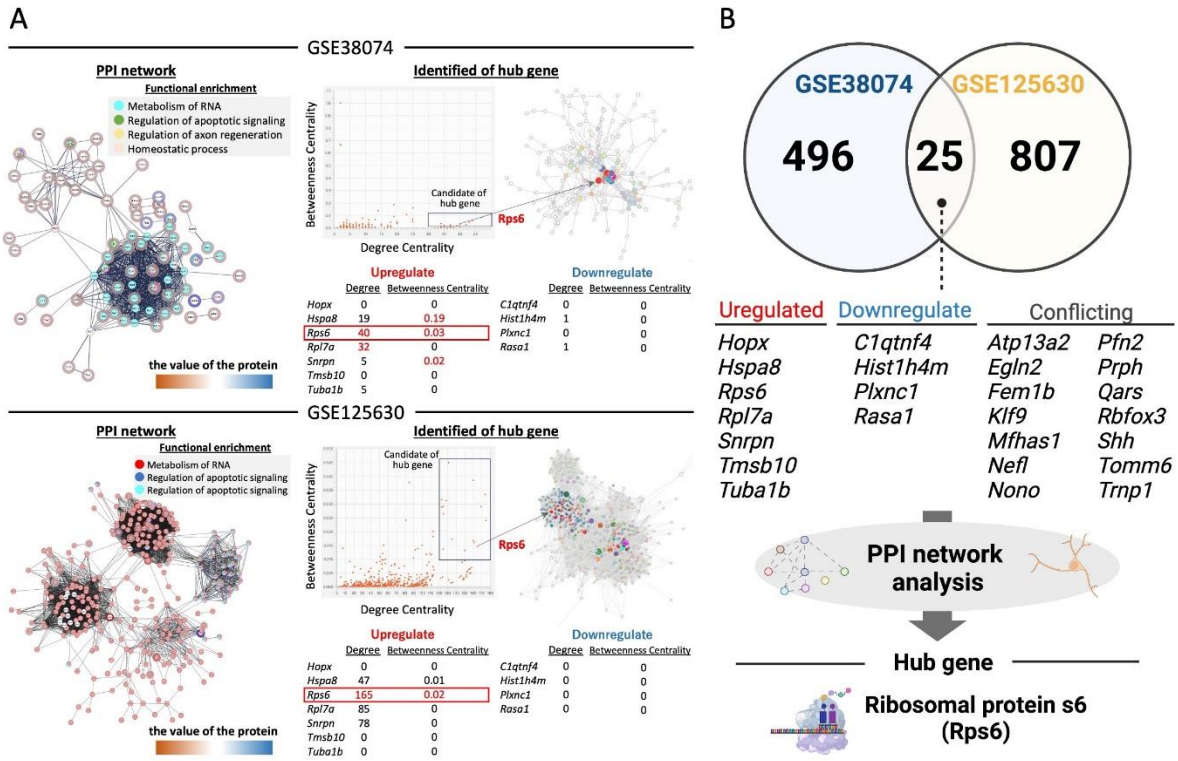
Program #/Poster #: PSTR116.20/VV48

Topic: I.02. Systems Biology and Bioinformatics

Title: Ribosomal protein s6: a hub gene mediating the effects of exercise in the sensory nervous system

Authors: *S. KAWABATA[1], H. IIJIMA[2], N. KANEMURA[3], K. MURATA[3];
[1]Grad. Sch. of Saitama Prefectural Univ., Saitama, Japan; [2]Nagoya Univ., Nagoya, Japan;
[3]Saitama Prefectural Univ., Koshigaya, Japan

Abstract: Objective: We began by understanding the absolute factors that indicate exercise by identifying the factors that have a central function in the complex network of various signaling pathways triggered by exercise in sensory nerves. **Methods:**Gene datasets (GSE38074 and GSE125630) were obtained. The TPM of each sample was determined. Differentially expressed genes (DEGs) based on the count data to estimate the significance of differences in gene expression between the exercise and control groups were detected. All DEGs were regarded as seeds for the construction of a Protein-Protein Interaction (PPI) network. The constructed network was topologically analyzed to define and identify hub genes based on degree and betweenness centrality for each dataset. **Results:**496 significant DEGs were detected in GSE38074 and 807 significant DEGs were detected in GSE125630. 25 DEGs were consistently detected in both datasets(Fig.1B). In GSE38074, degree > 30 and betweenness centrality > 0.01 were defined as candidate hub genes, and Ribosomal protein s6 (Rps6) was identified as a hub gene (degree = 40, betweenness centrality = 0.03). In GSE125630, degree > 120 and betweenness centrality > 0.01 were defined as a candidate hub gene, and Rps6 was identified as a hub genes (degree = 165, betweenness centrality = 0.015)(Fig.1A). In both PPI networks with DEGs detected in the two extracted datasets, Rps6 was identified as a hub gene with the ability to mediate the effects of exercise (Fig.1B). **Discussion:**the post-translational modification of Rps6 by phosphorylation has been shown to be essential for peripheral and central nervous system regeneration. In this study, using the PPI network, we found that Rps6 plays a functional hub role in mediating the effect of exercise. This suggests that exercise contributes to the prevention and improvement of sensory nerve degeneration through the Rps6. **Conclusion:**Rps6 is a hub gene that mediates the effects of exercise on the sensory nervous system.



Disclosures: **S. Kawabata:** None. **H. Iijima:** None. **N. Kanemura:** None. **K. Murata:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.21/VV49

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Functional validation of RNAscope for TRPA1

Authors: *C. I. CIOTU[1], N. S. ROJAS-GALVAN[2], S. HEBER[1], M. J. M. FISCHER[1];
[1]Med. Univ. of Vienna, Vienna, Austria; [2]King's Col. London, London, United Kingdom

Abstract: The potential of the transient receptor potential ankyrin 1 channel (TRPA1) as a therapeutic target for analgesic and non-analgesic disease-modifying drugs relies on its expression in both neuronal and non-neuronal cells. However, the lack of specificity in commercially available TRPA1 antibodies has hindered the understanding of its distribution and its role in physiology and disease mechanisms. In this study, we explored the use of RNAscope, an RNA-based technique that bypasses the need for antibody-based protein detection, to achieve higher sensitivity and specificity in detecting functional TRPA1. Qualitatively, our results demonstrate that the functional response of TRPA1 and the fluorescent signals from RNAscope

co-localized in sensory neurons. Additionally, we observed that the functional response of TRPV1, another ion channel, also co-localized with the RNAscope staining signal specific to TRPV1 in sensory neurons. Furthermore, we detected the presence of TRPA1 and TRPV1 mRNA in the outgrowing neurites of dorsal root ganglion (DRG) neurons. As there is by far not a 1:1 equivalent between RNA and functional protein, the usefulness of a quantitative RNA-based detection requires validation. The results show a relevant positive association between the functional responses of TRPA1 and TRPV1 and their corresponding mRNA levels. This suggests that RNAscope might be the currently best option to study the distribution of TRPA1. This might apply to other targets with known issues of antibody-based detection. The higher sensitivity and specificity offered by RNAscope can enhance our understanding of the role of TRPA1 in various physiological processes and disease pathomechanisms.

Disclosures: C.I. Ciotu: None. **N.S. Rojas-Galvan:** None. **S. Heber:** None. **M.J.M. Fischer:** None.

Poster

PSTR116. Genomics, Proteomics and Bioinformatic Approaches

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR116.22/VV50

Topic: I.02. Systems Biology and Bioinformatics

Support: Chen Institute Graduate Innovator Grant

Title: Time-resolved analysis of protein expression in response to ketamine treatment

Authors: *S. MILLER[1], Z. BLUMENFELD[2], A. L. NICHOLS[3], H. A. LESTER[2], D. A. PROBER[3], D. A. TIRRELL[1];
[1]Chem. Engin., [2]Biol., [3]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Ketamine has received increasing attention for its promise as a rapid acting antidepressant, and in 2019, it was approved by the FDA in a nasal spray form for treatment-resistant depression. Whereas selective serotonin reuptake inhibitors (SSRIs), the current first-line treatment for depression, are characterized by a “therapeutic lag” of 2-6 weeks and are only effective in about two-thirds of patients, sub-anesthetic doses of ketamine have been shown to produce relief from depressive symptoms as soon as one hour after administration that can last up to a week. While ketamine’s dissociative effects are known to be mediated via non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonism, the mechanism by which it functions as an antidepressant at lower doses remain unclear. Proteomic techniques provide powerful insights into how cells or organisms respond to drugs at the molecular level by identifying all proteins present in a sample and how they change in response to treatment. However, traditional proteomic methods do not provide information about when proteins were synthesized, making it impossible to distinguish proteins produced in response to the drug from preexisting proteins that were made prior to treatment. In this work, we use bioorthogonal

noncanonical amino acid tagging (BONCAT) to label and enrich proteins synthesized during the first 12-24 hours of ketamine treatment, both *in vitro* in cultured primary embryonic rat cortical neurons and *in vivo* in zebrafish larvae. Newly synthesized proteins labeled with azidohomoalanine (AHA), a chemically tagged methionine analog, were affinity purified for subsequent proteomic analysis via liquid chromatography-tandem mass spectrometry (LC-MS/MS). Over multiple experiments both *in vitro* (4 million cortical neurons per sample, n=4-5 per experiment, ~8000 proteins identified) and *in vivo* (150 pooled wild type zebrafish larvae per sample, n=3-4 per experiment, ~4000 proteins identified), we have observed previously reported increases in overall protein synthesis in response to ketamine treatment. In addition to identifying proteins that past studies have connected to ketamine, we have identified hundreds of significantly differentially expressed proteins and pathways that have not previously been implicated in ketamine's antidepressant effects, providing new insights into its mechanism of action. These results open the door to further mechanistic analyses, such as through the use of genetic tools to knock out or overexpress proteins of interest identified in this work, to clarify the role that differentially expressed proteins play in mediating ketamine's antidepressant effects.

Disclosures: **S. Miller:** None. **Z. Blumenfeld:** None. **A.L. Nichols:** None. **H.A. Lester:** None. **D.A. Prober:** None. **D.A. Tirrell:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.01/VV51

Topic: I.04. Physiological Methods

Support: NIH/NINDS (R01-NS090874)
NIH/NINDS (R01-NS101013)
NIH/NIBIB (R01-EB026439)
NIH/NIBIB (P41-EB018783)
NIH/NINDS (U24-NS109103)
NIH/NINDS (U01-NS108916)
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NIH/NINDS (R25-NS090978)
NREF & L. Nelson "Nick" Hopkins Research Fellowship Grant jointly sponsored by Arvind Ahuja, MD, FAANS, and the AANS/CNS Cerebrovascular Section

Title: Concurrent electrophysiological and hemodynamic monitoring of visual cortex using implanted multimodal electrodes

Authors: *A. I. SRIENC[1], A. AGATO[2], P. DEMAREST[3], J. W. TROBAUGH[4], M. ADAMEK[5], S. A. ANAND[3], D. W. MORAN[3], J. T. WILLIE[1], P. BRUNNER[1], J. CULVER[2]; [1]Neurosurg., [2]Dept. of Radiology, [3]Dept. of Biomed. Engin., [4]Dept. of Electrical and Systems Engin., Washington Univ. in St. Louis, Saint Louis, MO; [5]Dept. of Neurosurg., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Stereoelectroencephalography (SEEG) with invasive depth electrodes is used for intracranial localization of seizure onset zones, functional stimulation mapping, and human neurophysiology research. SEEG provides gold-standard seizure measures but has limited spatial sampling. By contrast, measuring cerebral hemodynamic activity by differential absorption of near-infrared light by oxy- vs deoxy-hemoglobin, may increase spatial sampling. We asked whether it is feasible to measure concurrent electrical and hemodynamic activity by modifying SEEG electrodes to contain optical fibers to create an invasive three-dimensional optical array of near-infrared sources and detectors integrated with depth electrodes. We sought to determine the feasibility of implanting SEEG electrodes with inserted optical fibers to measure electrophysiological responses while monitoring concurrent hemodynamic signals. Two Rhesus macaques were each implanted with a parallel array of 12 clinical SEEG electrodes (PMT, Inc.) in the occipital lobe. An optical fiber was inserted into each electrode so the tip of the fiber terminated between contacts to introduce 850 nm light into the tissue. Cortical activation was elicited with visual and electrical stimulation. A terminal trial was performed during which measurements were made while infusing a lethal dose of pentobarbital. Visually- and electrically-evoked potentials were successfully recorded from the occipital lobe at all recording sites. Concurrent hemodynamic measurements with the optical fibers detected hemodynamic signals that were temporally correlated with visual stimulus presentation. During the terminal trial, electrical and hemodynamic responses dissipated within seconds of cardiac arrest. We thereby demonstrate that an array of optical fibers integrated within SEEG electrodes can detect functional hemodynamic responses while SEEG electrodes can concurrently detect visually- and electrically-evoked potentials in the macaque occipital lobe. This suggests that an integrated multimodal system can be used for concurrent electrical and hemodynamic monitoring during brain activity. Future studies will determine the relationships of electric potentials to hemodynamic activity in eloquent cortices and epileptogenic networks in epilepsy patients.

Disclosures: A.I. Srienc: None. **A. Agato:** None. **P. Demarest:** None. **J.W. Trobaugh:** None. **M. Adamek:** None. **S.A. Anand:** None. **D.W. Moran:** None. **J.T. Willie:** 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.; Inner Cosmos, Inc.. F. Consulting Fees (e.g., advisory boards); Medtronic, Inc.; Clearpoint Neuro, Inc.; Neuropace, Inc.; AiM Medical Robotics, Inc.. **P. Brunner:** None. **J. Culver:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.02/VV52

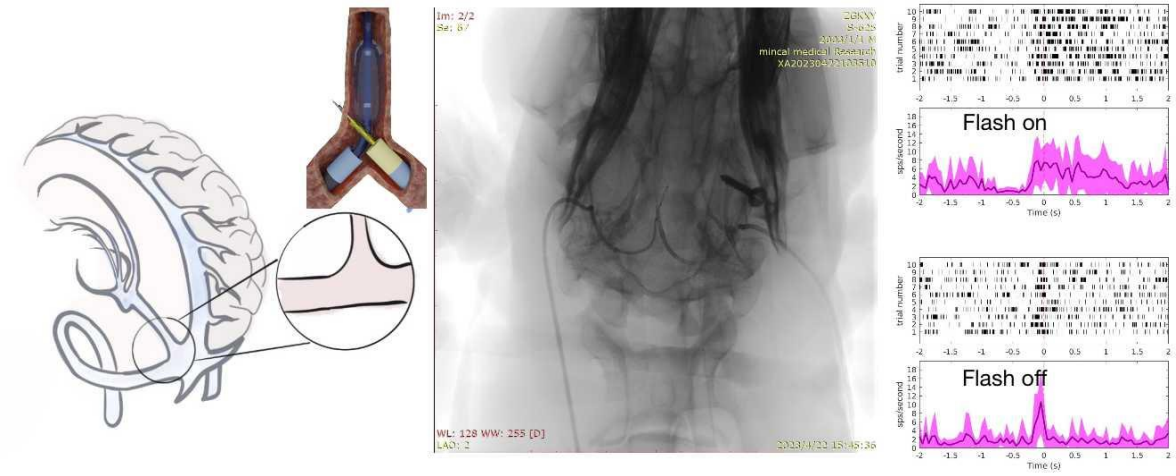
Topic: I.04. Physiological Methods

Support: E154NB1911

Title: Minimally invasive and ultra-flexible endovascular electrode for acute recordings of cortical activity

Authors: *X. WANG[1], Z. YANG[2], Y. BAO[1], S. WU[1], H. YANG[2], C. REN[1], Z. ZHAO[1];
[1]Chinese Acad. of Sciences', Shanghai, China; [2]Zhongshan Hosp., Shanghai, China

Abstract: The utilization of implantable neuroelectronic interfaces has yielded significant advancements in both fundamental research and the therapeutic management of neurological disorders. Nevertheless, conventional intracranial depth electrodes necessitate invasive surgical procedures for their placement, which can potentially impede the functionality of neural networks during the implantation process. The development of high-fidelity intracranial electrode arrays, designed for the purpose of recording and stimulating brain activity, has played a pivotal role in driving forward the treatment of neurological conditions over the past decade. However, the conventional arrays require direct implantation into the brain through open craniotomy, thereby giving rise to inflammatory tissue responses. Consequently, there exists a pressing need to explore minimally invasive approaches that circumvent the risk of brain trauma in order to effectively address these challenges.In this study, we present the successful demonstration of the feasibility of acute brain activity recording within a sheep vein utilizing an ultra-flexible and minimally invasive endovascular neural electrode. The system's design and properties have been meticulously developed and tailored to fulfill the essential requirements for effective delivery and implantation into brain blood vessels that are typically challenging to access using conventional devices. Through in vivo electrophysiology techniques, we were able to selectively record local field potentials and single unit spikes in the primary visual cortex, exhibiting a strong correlation with eye stimulation. Following subsequent histological and imaging analyses, it was observed that the tissue interface displayed minimal immune response and exhibited rapid recovery capability. The adaptable nature of this platform technology holds promise for potential extensions into the realm of neuroscience research tools and medical devices, with the primary goal of detecting and providing stimulation for neurological disorders.



Disclosures: **X. Wang:** None. **Z. Yang:** None. **Y. Bao:** None. **S. Wu:** None. **H. Yang:** None. **C. Ren:** None. **Z. Zhao:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.03/VV53

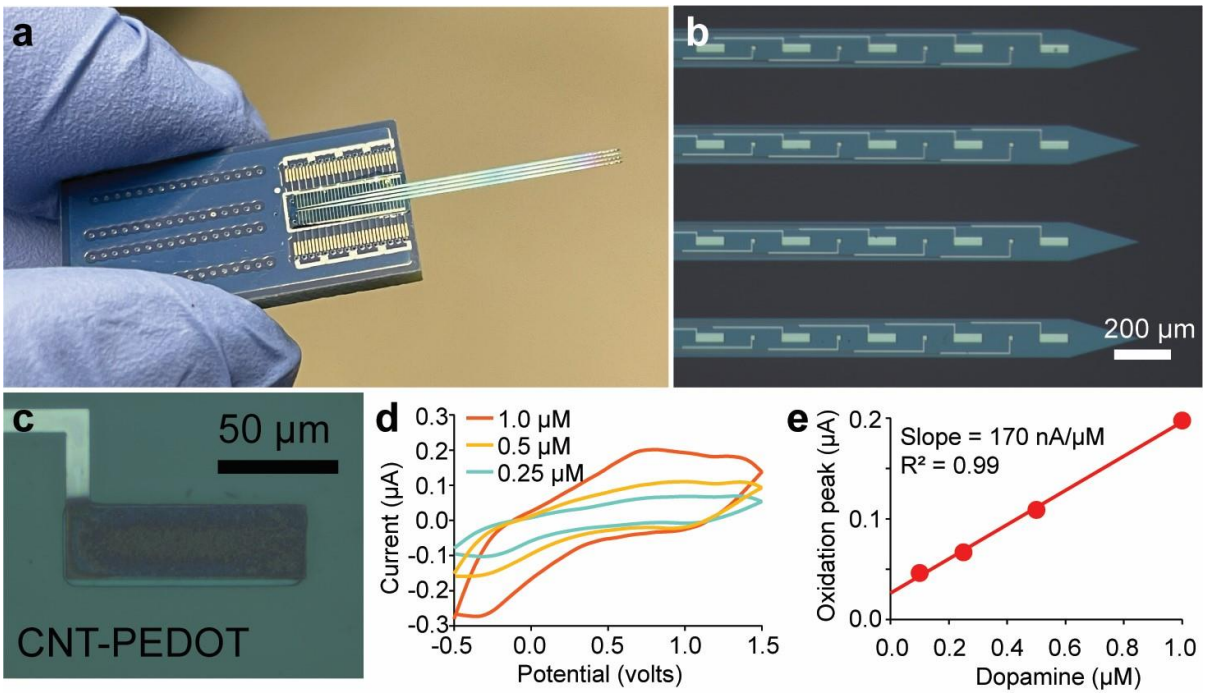
Topic: I.04. Physiological Methods

Support: NSF Grant 2133225
NSF Grant 2143140

Title: Carbon-based high-density multi-modal neural probe system for neural spike and dopamine mapping

Authors: K. A. WHITE, M. DARROUDI, ***B. N. KIM**;
Dept. of Bioengineering, The Univ. of Texas at Dallas, Richardson, TX

Abstract: Dopamine (DA) accounts for approximately 80% of the catecholamine content found in the brain. It plays a crucial role in cognitive processes and behaviors driven by reward. Our understanding of the intricate distribution of dopamine innervation in the brain is still in its early stages. Therefore, there is a critical demand for a novel neurotechnology capable of accurately mapping the spatial and temporal distribution of neurochemicals. Existing technologies including carbon-fiber electrodes and neurochemical fMRI suffer from low temporal resolution. In this work, we developed a carbon-based high-density multi-modal neural probe system that is capable of monitoring both dopamine activities and neural spikes activities. The probe integrates 64 neuroelectrodes (32 neurochemical electrodes and 32 electrophysiology electrodes, Figure a-b). The neurochemical electrodes are coated with carbon nanotubes (CNT) and PEDOT:PSS in order to carbonize the surface for high stability during recordings (Figure c). The carbonized electrode is tested by performing fast-scan cyclic voltammetry (200 V/s scan rate, -0.5 - 1.5V, 10 Hz frequency) which showed high DA sensitivity (170 nA/μM, Figure d-e). This is ~4 times more sensitive compared to a typical carbon-fiber microelectrode with an identical surface area. The presented multi-modal neural probe system includes a custom-designed headstage that can record simultaneously from 32 neurochemical electrodes and 32 electrophysiology electrodes. With the high spatiotemporal resolution, the novel multi-modal neural probe can be used to identify the distinct role of heterogeneous distribution of dopamine, both spatially and temporally, in neuromodulations including directing motor control, motivation, reward, and cognitive function.



Disclosures: **K.A. White:** None. **M. Darroudi:** None. **B.N. Kim:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.04/VV54

Topic: I.04. Physiological Methods

Title: Measuring correlations between motor and visual cortex with dual 1024-channel Neuralink implants in freely-moving macaques

Authors: A. LEBEDEVA[1], A. D. WONG[2], K. KOVACIC-TAYLOR[2], J. E. O'DOHERTY[2], K. D. HARRIS[1], M. CARANDINI[1], *D. L. ADAMS[2];
[1]Univ. Col. London, London, United Kingdom; [2]Neuralink, Fremont, CA

Abstract: Work in rodents has revealed signals that are shared widely across the brain, related to movements and internal state. For instance, the primary visual cortex (V1) of the mouse carries strong signals associated with running, whisking, and movements, both instructed and uninstructed. There is debate as to whether a similar sharing of global signals is present in the primate brain. To date, neuronal signals from multiple brain regions in freely moving primates have been difficult to record. We analyzed data gathered during testing of the Neuralink implant

in two freely-moving macaques, each with 1024-channel implants in V1 and in the arm representation of primary motor cortex (M1) in contralateral hemispheres. Thin-layer electrodes recorded extracellularly from single neurons and transmitted 15 ms binned spike counts wirelessly to a computer. Recordings were made while macaques were unrestrained in their home environment during normal behavior, sleeping, or performing visual and motor tasks: a joystick-controlled game or a saccade-to-target task for food reinforcement. Gaze direction was recorded at 120 Hz using an infrared eye tracker. V1 receptive fields were mapped using reverse correlation, and M1 signals were correlated with movement of the right arm.As expected, activity in V1 was strongly correlated with visual stimuli and saccades. The receptive fields of the recorded V1 units were highly localized and consistent even when recorded 10 days apart, indicating that the activity in this area was preserved across days. Activity in M1 was strongly correlated with arm movements, as well as with saccades. The correlations between units recorded within each area were strong and highly significant, and the strength of this correlation depended on the behavioral state and the specific task, and was consistent across days. Correlations between units in V1 and M1 were much smaller, but were significant for a minority of pairs of units, depending on the behavioral task.These results suggest that cortical activity in primates exhibits a higher degree of localization compared to cortical activity in rodents. Further investigations into the underlying mechanisms and functional implications of this distinction between primate and rodent cortex may provide valuable insights into the evolution and specialization of cortical circuits across different species.

Disclosures: **A. Lebedeva:** None. **A.D. Wong:** A. Employment/Salary (full or part-time):; Neuralink. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralink. **K. Kovacic-Taylor:** A. Employment/Salary (full or part-time):; Neuralink. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralink. **J.E. O'Doherty:** A. Employment/Salary (full or part-time):; Neuralink. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralink. **K.D. Harris:** None. **M. Carandini:** None. **D.L. Adams:** A. Employment/Salary (full or part-time):; Neuralink. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralink.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.05/VV55

Topic: I.04. Physiological Methods

Support: NIH 1R21MH131527-01

Title: Custom Design and 3D Printed Skull Cap with Integrated Micro-drives for Multi-region Microelectrode Array Implantation for Rat Brain Recordings

Authors: *J. HARTNER[1], D. YI[2], H. ZHU[2], B. WATSON[1], L. CHEN[2];
[1]Univ. of Michigan Molec & Behav Neurosci Inst. (MBNI), Ann Arbor, MI; [2]Univ. of Massachusetts - Lowell, Lowell, MA

Abstract: Simultaneous chronic recording from multiple brain regions at high temporal resolution in freely behaving animals is a powerful method to deepen our understanding of brain dynamics. However, such experiments are limited by the labor-intensive procedures including repeated single-implant craniotomies, tedious stereotactic-based positioning of the miniaturized implants, and manual handling / fixations of the connecting electronics for each implant. To address these problems, we developed a digitally designed and 3D-printed skull cap with predetermined “craniotomies” and above-skull carriages for accurate but simplified multi-region recordings. This system can work for both multi-electrode arrays (MEAs) of single wires and silicon probe arrays.
For microwire (MEAs), a 32-channel 4-MEA (eight 50 μm tungsten wire each built by our benchtop approach) was tested through Sprague Dawley rat recordings. Our skull cap design CT-scan conforms tightly onto multiple rats of various size, age, and weight with minimal bregma alignment variance. The cap was designed with four predetermined openings (“craniotomies”) to enable implantation across a wide range of cortical areas, with edges for insertion location alignments and steps for insertion depth control, which dramatically reduced the manual surgical effort needed for alignment and positioning. The inserted 32-channel system was able to record spiking activities over 5 months across a 2D tiling of the cortical surface.
For silicon probes, we designed, printed and assembled skull caps with two embedded micro-drives for inserting two Buzsaki64 probes into hippocampus (HC) and prefrontal cortex (PFC). The HC and PFC insertion slots were designed based on a standardized bregma on the headcap, and the probes were affixed to the embedded drives prior to surgery, eliminating the need for stereotactic guidance and insertion during surgery. Probe depths were controlled with micro-drive lead-screw structures during both initial implantation and post-surgery final targeting. The prototyped two-probe system yielded high-quality spiking activity recording over weeks. The prototype headcap markedly reduced surgical time and burden by eliminating typical post-implantation steps for support structures.
Our 3D printed skull cap improved the surgical efficiency and therefore practicality for multi-implant electrophysiological recording experiments and the ability to repeatably implant large numbers of MEAs at custom locations. This implantation system may serve as a platform towards our ultimate goal of automated brain surgeries for large scale brain-wide insertion of miniaturized microelectrodes.

Disclosures: **J. Hartner:** None. **D. Yi:** None. **H. Zhu:** None. **B. Watson:** None. **L. Chen:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.06/VV56

Topic: I.04. Physiological Methods

Support: NIH Grant NS107667

Title: Advances in flexible microelectrode arrays via fabrication and insertion techniques

Authors: *A. M. YORITA[1], J. GLEICK[1], X. XU[1], J. ZHOU[1], M. JUTRAS[2], A. MALLORY[2], J. W. RUECKEMANN[2], E. BUFFALO[2], L. M. FRANK[3], R.-U. HAQUE[1];
[1]Lawrence Livermore Natl. Lab., Livermore, CA; [2]Univ. of Washington, Seattle, WA; [3]Dept. of Physiol., UC San Francisco, San Francisco, CA

Abstract: In order to record and track long-term (weeks to months) neural activity, improvements in implantable microelectrode arrays are needed to further improve performance and reduce tissue damage. We have designed, fabricated, and distributed flexible microelectrode arrays for a variety of species, e.g. rat, mouse, songbird, and non-human primate models. Additional engineering improvements continue to advance our array technology. With all animal models, we utilize microfabricated insertion shuttles to enable implantation of our flexible arrays. The ability to reduce insertion force during implantation is crucial towards improving recording quality. We have previously demonstrated that patterning the tip of the insertion shuttle in three dimensions reduces insertion force. Recently, we have leveraged novel microfabrication techniques to improve the patterning and etching steps of the insertion shuttle. Additionally, as our implantable technology moves towards higher channel counts and higher channel densities, we have looked at alternate electrode surface modifications to lower impedance with wafer-scale deposition and patterning. Overall, our efforts seek to push implantable technology development as we develop modular, high-density interfaces to further understand complex neural processes. Prepared by LLNL under Contract DE-AC52-07NA27344.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.07/VV57

Topic: I.04. Physiological Methods

Support: NIH Grant 1U01NS113252-01

Title: Ultra-high density electrode arrays for improved detection, stability, and cell type specificity in electrophysiological recordings

Authors: *A. M. SHELTON[1], Z. YE[3], J. COLONELL[4], J. BOUSSARD[5], J. SHAKER[3], L. PANINSKI[6], J. SIEGLE[1], C. KOCH[7], S. OLSEN[2], T. HARRIS[8], N. A. STEINMETZ[3]; [1]Neural Dynamics, [2]Allen Inst., Seattle, WA; [3]Univ. of Washington, Seattle, WA; [4]Janelia Res. Campus, Ashburn, VA; [6]Statistics, [5]Columbia Univ., New York, NY; [7]Allen Inst. For Brain Sci., Seattle, WA; [8]HHMI JRC, Ashburn, VA

Abstract: To study the neural basis of behavior, we require methods to sensitively and accurately measure neural activity at single neuron and single spike resolution. Extracellular electrophysiology is a principal method for achieving this but has biases in the neurons it detects and imperfectly resolves their action potentials. To overcome these limitations, we developed a silicon probe with significantly smaller and denser recording sites than previous designs, called Neuropixels Ultra (NP Ultra). This device takes advantage of the Neuropixels (NP) technology platform, allowing for hundreds of small, low-noise recording sites to be simultaneously sampled, thus capturing neuronal activity at ultra-high densities (>1300 sites per mm, 10 times higher than previous probes). NP Ultra, therefore, effectively comprises an implantable voltage-sensing camera that provides a complete planar image of the electrical fields generated by single neurons. As a result of this increased site density, NP Ultra probes provide substantially improved spatial resolution of individual action potentials across multiple brain regions and species. Here, we show that this unprecedented resolution enhances several different aspects of extracellular electrophysiology, including spike sorting performance, recording stability, and cell-type specificity.

Disclosures: A.M. Shelton: None. **Z. Ye:** None. **J. Colonell:** None. **J. Boussard:** None. **J. Shaker:** None. **L. Paninski:** None. **J. Siegle:** None. **C. Koch:** None. **S. Olsen:** None. **T. Harris:** None. **N.A. Steinmetz:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.08/VV58

Topic: I.04. Physiological Methods

Support: NSF CAREER
NSF GRF

Title: Polymer-based dual-sided microelectrode array for neurophysiological recording in small animal models

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Abstract: Neural electrophysiological recording in small animals is a crucial tool in neuroscience, providing valuable insights into how these cells communicate and process information. However, the design and fabrication of polymer-based high-density microelectrode arrays (MEAs) within a limited area remains challenging. Here, we introduce an innovative polymer neural probe, utilizing a dual-sided fabrication process that has the potential to markedly amplify the number of electrodes within a small area (250 µm by 100 µm). This innovative method places microelectrodes on both sides of the MEA, effectively doubling the electrode number and enabling dual-sided recording sites. Current MEA prototypes, with a diameter of 20µm, along with trace width and trace space of 20µm, yield a density of 327-348 channels/mm^2 for our 4-channel, 6-channel, and 8-channel configurations. We also used a mirror design for the contact pads, so that after the MEAs are folded in half, the contact pad overlaps. This facilitates the soldering process and increases the stability of the connection. By utilizing Parylene C as the substrate and encapsulation material, we were able to achieve good mechanical flexibility of the MEAs. By coating the gold electrodes with PEDOT: PSS, we were able to reduce the 1 kHz impedance from approximately 2.7 MΩ to about 110 kΩ. The microelectrode arrays are soldered onto a custom-made printed circuit board (PCB) which is linked to an Intan recording system (C3100, Intan Technologies, CA). We conducted *in vivo* recording by inserting our MEA approximately 100 µm into the antenna lobe of an insect (locust) brain, and successfully recorded extracellular neural responses from the projection neurons in the antennal lobe. Our data shows that this new electrode configuration is effective for recording from multiple projection neurons, simultaneously and preserves the characteristic spike shape of projection neurons. Our results demonstrate how these recording electrodes help distinguish multiple odorants at low concentrations (1% v/v). Ongoing research is also focused on improving the channel count and electrode density in the same area that covers the insect antennal lobe (~ 500 µm in diameter) and compare the odor-evoked population neural responses corresponding to different electrode configurations. Our innovative method allows for the fabrication of flexible polymer-based dual-sided MEAs with increased electrode density and the capability of high-resolution *in vivo* recording of neural activities in small animal brains.

Disclosures: X. Liu: None. **Y. Gong:** None. **S. Sanchez:** None. **G. Banna:** None. **D. Saha:** None. **W. Li:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.09/VV59

Topic: I.04. Physiological Methods

Support: NIH U01NS126046

Title: Development of a Design Library of Polymer-based Microelectrode Arrays for Rodent Multi-region Hippocampal Recordings

Authors: *H. XU[1], X. WANG[2], Y. GAO[1], T. ZHOU[1], E. MENG[1], D. SONG[1];
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Abstract: Obtaining long-term, stable recordings from anatomically and functionally connected brain regions of behaving animals is the foundation for studying brain functions. As one essential tool, conformal penetrating polymer microelectrode arrays (pMEAs) enabled direct access to individual neurons in multiple brain regions. Recently, advances in pMEAs demonstrated year-long recordings from neurons in rodent brains. However, access to pMEAs is greatly limited to selected groups with advanced nano-fabrication capabilities. To broaden the accessibility and promote the development of pMEAs, we are developing a library of pMEA designs covering various cortical and sub-cortical regions of the brains of mice, rats, and nonhuman primates (NHPs). We start with the hippocampus, a brain region that is of great interest in neuroscience and neural engineering and has a complex anatomical structure with distinct subregions. Two 3D hippocampal multi-region pMEAs are designed for rats. Design A consists of two four-shank MEAs with 64 channels in each MEA. One MEA targets the CA1 and the dentate gyrus (DG) subregions, while the second MEA, which is 1500 μm lateral to the first one, targets the CA1 and the CA3 subregions. Electrodes on each shank are divided into two recording groups with electrode layouts conforming to the curvature of hippocampal cell body layers. Design B consists of four two-shank MEAs with 32 channels in each MEA. Two MEAs are assembled back-to-back to enable double-side recordings. Like design A, the MEAs conform to the DG, CA3, and CA1 subregions. For mice, design A and B are reduced to four-shank 32-channel MEAs conforming to the cell body layers on a coronal hippocampal plane. These pMEA designs will be fabricated and delivered to expert users for reviews and feedback. Optimization of the pMEAs will be performed iteratively. Implantation methods for pMEAs with different lengths (5 to 40 mm), e.g., dip-coating and insertion shuttles, will also be developed and evaluated.

Disclosures: H. Xu: None. **X. Wang:** None. **Y. Gao:** None. **T. Zhou:** None. **E. Meng:** None. **D. Song:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.10/VV60

Topic: I.04. Physiological Methods

Support: ERC Consolidator Award 818179
SNSF CRSII5_198739/1

Title: Cortico-hippocampal coupling during ripples investigated at single-unit resolution with months-long-stable ultra-flexible low-impedance electrode arrays

Authors: *T. YASAR[1,2], P. GOMBKOTO[2], A. L. VYSSOTSKI[2], A. VAVLADELI[2], B. WU[2], L. MEIENBERG[2], V. LUNDEGARDH[2], W. VON DER BEHRENS[2], M. F. YANIK[2]; [1]D-ITET, ETH Zurich, Zurich, Switzerland; [2]Inst. of Neuroinformatics, ETH Zürich, Zürich, Switzerland

Abstract: While the number of channels in state-of-the-art in vivo electrophysiology systems is rapidly increasing, these technologies generally use stiff materials. The mechanical mismatch between these probes and the brain causes long-term damage to the brain tissue, limiting the longevity and quality of recordings. To address this challenge, we developed massively parallel flexible intracortical microelectrode arrays with a minimal footprint (MultiBundle arrays). In this study, we fabricated ultra-flexible intracortical microelectrode arrays which can be delivered into multiple brain areas at arbitrary locations with practically no depth limitations at a speed of 12.5 µm/s, using a novel strategy. In these arrays, each channel is mechanically independent to provide maximal compliance with the brain tissue—while also allowing to pack a high density of channels within a minimal footprint at each brain area, with 256 channels in total. During the fabrication of our devices, we robustly achieve 54±16 kOhm impedances for electrode pads with 13x13 μm^2 surface area and 2.4 µm thickness. We performed simultaneous recordings from the medial prefrontal cortex (mPFC), retrosplenial cortex (RSC), dorsal hippocampus (dHPC), and intermediate hippocampus (iHPC) in freely moving rats (n=5). We recorded stable single-unit activity with the MultiBundle arrays while tracking some units putatively for up to 3.5 months. Immunostaining of brain slices revealed no significant long-term damage caused by the electrodes to the surrounding brain tissue. With this technology, our investigation focused on the cortico-hippocampal coupling at the single-unit level during hippocampal sharp-wave ripples (SPW-Rs). We identified different subclasses of hippocampal ripples according to their location, frequency decomposition, and associated ensemble activity patterns in mPFC and RSC. These findings suggested the presence of distinct cortical assemblies that selectively respond to individual shape-wave ripples in the two investigated cortical areas. Furthermore, the ability to track single units with our stable recordings allowed us to identify and track neuronal assemblies in mPFC and RSC, which exhibited varying preferences towards specific SPW-Rs. Currently, we are expanding the scope of our electrode arrays and recording electronics to encompass a broader range of brain areas, enabling wireless and untethered recordings with a higher number of channels.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.11/VV61

Topic: I.04. Physiological Methods

Support: RS-2020-KD000103

Title: Hippocampal-focused ultrasound stimulation induces alterations in theta and gamma oscillation in the medial prefrontal cortex

Authors: *J. BAEK[1,3], Y. SEO[3,2], W. CHANG[3];
[2]Grad. Sch. of Med. Science, Brain Korea 21 Project, [1]Yonsei Univ., Seoul, Korea, Republic of;
[3]Yonsei University, of Med., Seoul, Korea, Republic of

Abstract: Introduce Neuromodulation is the alteration of nerve activity through the targeted delivery of a stimulus, and it is carried out to normalize or modulate nervous tissue function. Recently, several reports suggested that Focused Ultrasound (FUS) stimulates neuronal activity and is effective in neuromodulation. The hippocampal formation (HPC) and medial prefrontal cortex (mPFC) have well-established roles in memory encoding and retrieval. During spontaneous behaviors, functional connectivity between the HPC and mPFC can be inferred from electrophysiological recordings of local field potentials (LFP). In this study, we will use a new electrophysiology tool, Neuropixel, to confirm the HPC-mPFC connection during FUS neuromodulation.
Method Fourteen male C57BL/6J mice were used. Mice were divided into The control group and The FUS group. In the FUS group, each mouse was neuromodulated in the hippocampus area for 20 minutes. FUS was sonicated with parameters of 515 kHz FF, 50% DC, 1 kHz PRF, 0.2 ms TBD, 300 ms SD, and 2 s ISI. The hippocampal activity was measured by inserting a Neuropixel probe into the mPFC of all mice. LFP was recorded during FUS neuromodulation and Pre and Post neuromodulation. The LFP data were sampled at 2500 Hz and analyzed using Matlab.
Result Changes in neural activity which was recorded by Neuropixel were measured and compared. Analyzed recorded LFP data by Neuropixel confirmed that the theta and gamma oscillation was enhanced in the mPFC after FUS neuromodulation. To confirm whether the historical result was corresponding to the electrophysiological result analyzed, mPFC and HPC were stained by immunohistochemistry. C-Fos, an indirect marker of neuronal activity was stained. FUS neuromodulation significantly enhanced c-Fos expression in the HPC and mPFC, showing that more neurons are engaged during FUS neuromodulation.
Conclusion Decades of research in both humans and animals have revealed that two brain areas, HPC, and mPFC, are essential for the encoding and retrieval of episodic memories. Recently, the HPC-mPFC interaction was demonstrated in electrophysiological results: Theta oscillations and Gamma oscillations. During the spatial working memory task, Theta and Gamma oscillations were increased with the learning of spatial working memory. This experiment confirmed that neural activity can be identified by using Neuropixel during FUS neuromodulation in the HPC. Via the result, it proved that brain waves can be measured using Neuropixel, and can employ simultaneously with FUS neuromodulation. In a further study, Neuropixel will be used as an electrophysiological tool to record various neurological diseases' neural activity.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Topic: I.04. Physiological Methods

Support: NIH Grant R44NS105500
NIH Grant R43AA030512
DARPA Contract HR0011-16-C-0094

Title: Ultrasonic Vibration of Neural Implants Decreases Insertion Force, Improving Implant Accuracy and Decreasing Insertion-based Tissue Damage

Authors: *R. BAGWELL[1], F. A. LI[2], J. A. GALLEGO[2], S. LEE[4], A. YORITA[5], J. K. GREASER[6], T. L. CARLSON[8], E. M. STEFFAN[6], C. A. SCRUGGS[7], K. A. SNOOK[6], K. W. GHERES[6], V. CUZON CARLSON[9], R.-U. HAQUE[5], T. D. KOZAI[3], M. L. MULVIHILL[6]; [1]Actuated Medical, Inc., Bellefonte, PA; [2]Dept. of Bionengineering, [3]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [4]Dept. of Neurol., Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [5]Lawrence Livermore Natl. Lab., Livermore, CA; [7]Res. and Develop., [6]Actuated Med. Inc., Bellefonte, PA; [8]Div. of Neurosci., Oregon Hlth. Sci. Univ., Beaverton, OR; [9]ONPRC/OHSU, Beaverton, OR

Abstract: The brain is an anisotropic tissue environment with cellular and fluid components that impact the ability to consistently and accurately insert devices to a desired target with minimal damage. This anisotropy impacts the placement of two critical neuroscience tools 1) Intracortical electrodes to study and modulate brain function and 2) infusion cannula used to deliver Adeno-Associated Virus (AAV) In the case of Intracortical electrodes, damage caused during the insertion process is the initiating event of the cellular foreign body response (FBR) responsible for the encapsulation of chronically implanted electrodes and loss of neuronal complexity and excitability around insertion sites. Low-speed insertion causes tissue dimpling and damage, and challenges with accurate placement. High-speed insertion methods reduce tissue deformation by minimizing CSF displacement, but compromise insertion depth accuracy and risk tissue trauma. To solve this issue, the project team designed and fabricated an oscillated insertion device paired with a high-resolution stepper motor allowing for micron-scale ultrasonic vibration of neural implants and constant velocity, low-speed insertion. The approach demonstrated significant reduction of insertion force for single-shank and multi-electrode arrays, reduced MRI and histological markers of tissue damage (tissue edema, cortical thinning, gliosis) and indicators of improved electrode-tissue contact (higher amplitude action potentials, decreased electrode capacitance). Additionally, oscillated insertion of flexible polyimide electrodes facilitates support-free insertion, enabling a simplified surgical approach for electrodes designed to minimize FBR during chronic recordings.For long (1cm+), thin (25-33G) AAV infusion cannula there are additional challenges. The primary issue is that the flexible cannula deflect as they traverse different tissue regions, making delivery of the AAV to the target difficult. Additional coupling approaches, between the actuator and cannula, were developed and evaluated.

Oscillated insertion of infusion cannula reduces overall insertion force 80-90%. Improvements in trajectory and accuracy of bolus delivery were evaluated in vivo and results were quantified using MRI and histological methods.These results demonstrate that vibrated insertion facilitates damage-free implantation of small diameter cannula and implants for intraparenchymal infusions and electrophysiology.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.13/VV63

Topic: I.04. Physiological Methods

Support: ChroMOS project: H2020-MSCA-IF-2019 (GA 896996).

Title: Performances of active CMOS-based SiNAPS neural probes up to 1024 simultaneoulsy recording electrode channels.

Authors: *G. ANGOTZI[1], J. F. RIBEIRO[2], G. ORBAN[2], A. PERNA[2,3], M. VINCENZI[2], F. BOI[4], L. BERDONDINI[2];
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Abstract: Performances of active CMOS-based SiNAPS neural probes up to 1024 simultaneously recording electrode channels**Authors*G. N. Angotzi**[1,2], J. F. Ribeiro[1], G. Orban[1], A. Perna[1,3], M. Vincenzi[1], F. Boi[2], L. Berdondini[1]; [1]Microtechnology for Neuroelectronics Laboratory, Fondazione Istituto Italiano di Tecnologia, Genova, Italy; [2]Corticale Srl, Genova, Italy; [3]The Open University Affiliated Research Centre at Istituto Italiano di Tecnologia (ARC@IIT), Genova, Italy**DisclosuresG. N. Angotzi**: holds equities in Corticale Srl. **J. F. Ribeiro**: None. **G. Orban**: None. **A. Perna**: None. **M. Vincenzi**: None. **F. Boi**: holds equities in Corticale Srl. **L. Berdondini**: holds equities in Corticale Srl.**Abstract**The SiNAPS technology is currently available worldwide to neuroscience researchers. This implantable active CMOS-based technology enables the recording of brain electrical activity from up to 1024 electrodes per probe at sub-milliseconds and cellular resolutions within and across superficial and deep brain circuits in multiple brain regions. Probes implement full-band DC-coupled electrode-pixel front-ends entirely integrated underneath each microelectrodes site (pitch < 30 µm) that are then grouped in modules of 32 closely spaced microelectrodes and a single connection line per module is achieved by the in-shank time division multiplexer. These features allow to rapidly meet neuroscientists requirements for device sizes, scalability, and probe layouts while sampling neural activity up to 20 kHz/microelectrode. Here, we will provide an updated overview of different layouts of implantable probes realized so far, including research prototypes and commercially available devices, and discuss their performances in different animal models and experimental conditions. Specifically, this includes single and multiple shank probes from 256 and up to 1024 simultaneously recording channels that were used in mice and rats in both acute and chronic conditions. Neural probes with up to 1024 electrodes specifically designed for non-human-primates (NHPs), and microwire-like probes (or ChroMOS probes) with cross-sectional shank sizes down to <30 µm to minimize tissue damage and the foreign body reaction when chronically implanted will also be presented.

Disclosures: G. Angotzi: A. Employment/Salary (full or part-time):; Corticale srl. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale srl. **J.F. Ribeiro:** None. **G. Orban:** None. **A. Perna:** None. **M. Vincenzi:** None. **F. Boi:** A. Employment/Salary (full or part-time):; Corticale srl. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale srl. **L. Berdondini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale srl.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Topic: I.04. Physiological Methods

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NIMH (R01 MH117777)
Simons Foundation (542955)
P51OD010425

Title: Chronic recordings from deep brain structures in monkeys using flexible, high-density probes

Authors: A. J. MALLORY[1,3], A. D. GARCIA[1,3], A. M. YORITA[4], R. HAQUE[4], L. M. FRANK[5], E. A. BUFFALO[1,3], *J. W. RUECKEMANN[2,1,3];
[1]Physiol. and Biophysics, [2]Univ. of Washington, Seattle, WA; [3]Washington Natl. Primate Ctr., Seattle, WA; [4]Lawrence Livermore Natl. Lab., Livermore, CA; [5]Dept. of Physiol., UC San Francisco, San Francisco, CA

Abstract: Deep brain areas in primates present unique challenges for chronic, high density electrophysiological recordings. Accurately targeting structures centimeters within the brain requires an implant that is rigid for insertion; however it must also be flexible to accommodate the brain movement that occurs in larger species and maintain recording stability.
We adapted flexible polyimide multicontact probes that have recorded stable, isolated neurons and local field potentials (LFP) for months at a time in rodents. For rigidity during implantation, the probe is attached via a dissolvable bioadhesive to a low profile, sharpened, silicon stiffener that minimizes damage during insertion. Once the probe is moved to the target structure, the adhesive dissolves and the stiffener is retracted. This leaves only the flexible probe in place that can match the movement of the brain, reducing neural damage and improving the stability of recordings. For use in monkeys, the probe was lengthened to reach deep targets, and the stiffener was reinforced to penetrate the more durable monkey pia mater while still retaining a slim profile.
A new surgical approach was innovated to accurately target deep brain structures and minimize damage during insertion. A surgical robot was used to guide the probe along a prescribed path to within one centimeter of the target using precalculated trajectories calibrated to a subject-specific MRI. Hydraulic micromanipulators mounted to the robot were then used during the final approach for a precise and smooth entry into the target structure. After the stiffeners were removed, the probes were encased in a flexible polymer and secured within a custom chamber robust to manipulation from monkeys. Two monkeys were implanted with multiple probes in structures more than 30mm from the skull surface including hippocampal subfield CA3 and the lateral geniculate nucleus. Additional probes were placed in superficial area 8a (FEF) of the prefrontal cortex. Targeting was confirmed by locating glial scars with immunohistochemical staining for GFAP. Isolated neurons and stable LFPs were recorded over a period of several weeks. The fixed spacing of the probe contacts allowed for current source density analysis of the LFP distinguishing intrinsic current sources from volume conducted noise.
This novel method will enable experiments that investigate single cell and LFP responses with chronic recordings from multiple brain areas in primates. By minimizing damage during implantation and facilitating stability of chronic recordings, this approach can be leveraged to support freely moving animals, 24-hour recordings, and eventually human biomedical applications.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

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Title: A Thin, Flexible, and Scalable MEMS based Depth Electrode for Deep Brain Recording and Stimulation

Authors: *K. LEE[1], A. PAULK[3], Y. RO[4], K. TONSFELDT[5], Y. TCHOE[2], A. BOURHIS[1], J. LEE[5], D. R. CLEARY[1], J. PEZARIS[6], Y. KFIR[7], S. S. CASH[8], S. DAYEH[9];
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Abstract: Electrocorticography (ECoG) and stereoelectroencephalography (sEEG) are the gold standard for recording intracranially in the human brain to help localize epileptogenic zone and determine the onset and propagation of epileptiform discharges in patients with intractable epilepsy. Yet, the spatial resolution, or contact spacing, most commonly used is on the scale of 1 cm in existing clinical ECoG grids and strips, and 3 - 6 mm in sEEG which could limit both the diagnostic and therapeutic benefits, such as using stimulation to map epileptogenic brain networks. To improve this spatial resolution and leveraging thin film processing with sacrificial layer deposition and etching, we developed a microelectrode-sEEG (μ-sEEG) with 128 platinum nanorod (PtNR) contacts which can achieve a minimum of 30 μm contact-to-contact spacing that can be implanted in deep brain structures. A monolithically integrated pocket on back side of the polymer electrode layers allowed us to insert a clinical grade stylet (1 - 180 mm -long-stylet) into the pocket to assist insertion of the flexible polymer electrode into deep brain structures. We

could also then retract the stylet after the insertion, consistent with standard clinical procedures in implanting sEEG electrodes. The entire μ-sEEG electrode is approximately 10 μm thick which resulted in minimal tissue damage in chronic implants when compared to standard clinical sEEG electrodes. Further, we designed multiple versions of the μ-sEEG device which could be used either acutely or in a chronic preparation and could be either only spanning the cortex (3-4mm long) or extend deep into primate cortex (10 cm long). We validated the performance of our μ-sEEG electrodes in laminar recordings in acute and chronic rat cortical preparations, acutely in the pig cortex, acutely in the operating room in the human cortex, and in deep subcortical structures in an acute non-human primate (NHP) preparation. As PtNR contacts can be made to be microelectrodes while maintaining low impedances (~300 kΩ), the implantable μ-sEEG device was able to record single unit activity along with physiologically-relevant broadband dynamics including low frequency oscillations and high-gamma activity as shown in the voltage dynamics and through current-source density (CSD) analysis. When validated for safety and efficacy in animals, the μ-sEEG electrode holds the potential for recording and disrupting local brain activity on the single cell level and may help understanding and treating epilepsy and beyond.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.16/WW2

Topic: I.04. Physiological Methods

Support: Wellcome Trust (204915)
Allen Institute

Title: A prototype Neuropixels Opto probe for simultaneous large-scale recording and optogenetics

Authors: ***K. Z. SOCHA**[1], A. A. LAKUNINA[2], A. BOWEN[3], B. KARSH[4], M. KRUMIN[1], J. O'CALLAHAN[5], P. NEUTENS[5], H. TILMANS[5], B. DUTTA[5], M. HAUSSER[1], N. A. STEINMETZ[3], K. SVOBODA[2], J. H. SIEGLE[2], T. HARRIS[4], M. CARANDINI[1];
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Abstract: Understanding the brain's code and circuits requires recording from myriad neurons of known genetic identity and manipulating their activity. For recordings, the gold standard is electrophysiology, which was recently transformed by Neuropixels probes. For manipulating and

identifying neurons, in turn, the best method is optogenetics, which requires delivering light. Currently, combining the two approaches is laborious, as one must either glue an optic fiber to a probe, or adopt optrodes that have few recording and emission sites or deliver low light intensities. We are therefore piloting a prototype integrated electronic and photonic Neuropixels Opto probe, which simultaneously records signals from 960 electrical sites and emits light from 14 emission sites (16-25 μm2 each) per wavelength, spaced ~100 μm apart. Light from external lasers is flexibly routed through a monolithically integrated silicon nitride photonics layer that lies on top of the active CMOS layers. This layer provides high-density photonic waveguides to the emission sites, which are apodized grating couplers that emit light perpendicularly to the probe into the tissue. The probe base contains the driver electronics and thermo-optic photonic switching circuits and modulation devices.Pilot experiments in mouse visual cortex indicate that the probe allows spatially addressable optogenetics with concurrent recordings with the same quality as current Neuropixels probes. We inserted Neuropixels Opto probes in the visual cortex following viral injection of a red-shifted opsin (ChRmine) in excitatory (CaMK2+) cells. Pulses of red light (638 nm) lasting 400 ms and randomized from trial to trial across emission sites elicited neural activity - simultaneously recorded on adjacent recording sites on the probe - that was spatially restricted to the site of emission. We then repeated the experiment with briefer, 10 ms pulses of light and found that we could successfully identify (optotag) excitatory cells.These results indicate that Neuropixels Opto probes can precisely manipulate the activity of local neural populations near emission sites. We anticipate that they will become an essential tool for combining high-density electrophysiological recordings with local optogenetic activation or inactivation. The next steps of the project will involve more rounds of design, fabrication, and thorough testing in vivo, aiming to explore possibilities to emit light at blue wavelengths (450 nm) and to minimize fabrication costs. Our goal is to release a finalized probe in 2028 using the same non-profit distribution model as current Neuropixels probes.

Disclosures: **K.Z. Socha:** None. **A.A. Lakunina:** None. **A. Bowen:** None. **B. Karsh:** None. **M. Krumin:** None. **J. O'Callahan:** None. **P. Neutens:** None. **H. Tilmans:** None. **B. Dutta:** None. **M. Hausser:** None. **N.A. Steinmetz:** None. **K. Svoboda:** None. **J.H. Siegle:** None. **T. Harris:** None. **M. Carandini:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.17/WW3

Topic: I.04. Physiological Methods

Support: Wellcome Trust (204915)
Allen Institute

Title: Recording and optotagging in the mouse striatum with prototype Neuropixels Opto probes

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Abstract: Neuropixels probes have transformed our ability to record spiking activity across the entire brain. As with all passive extracellular electrophysiology devices, Neuropixels are limited in their ability to ascertain the genetic identity of the neurons being recorded. Optotagging, whereby a cell type of interest is induced to express a light-sensitive opsin, remains the gold standard method for identifying specific cell types in electrophysiology experiments. Performing optotagging with Neuropixels currently requires colocalization of recording sites and an external light source and produces a significant photoelectric artifact. This limits the utility of Neuropixels for cell type-specific recordings, especially in deep structures. These limitations were an important motivation for us to develop Neuropixels Opto, a probe designed to facilitate dual color optotagging in any brain region without the need to implant an optical fiber. The prototype version of these probes use the same electronics backend as Neuropixels 1.0 (960 recording sites arrayed in two columns with 20 µm vertical spacing), with the addition of photoemission sites for delivering light at two wavelengths (14x2 layout with 100 µm site-to-site spacing). Light from external lasers is routed to the shank via high-density photonic waveguides. Light is then reflected into the surrounding tissue by grating couplers engineered to illuminate the majority of neurons within the listening radius of the recording sites. As a proof of concept, we used these probes with red light (638 nm) to optotag genetically identified populations of direct and indirect pathway medium spiny neurons in the mouse striatum. Our experiments confirm that the pilot Neuropixels Opto probe allows optotagging with nearly undetectable artifacts. Compared to light delivered via the brain surface, off-target network effects are greatly reduced. The most effective photoemission site for optotagging is the one closest to a neuron's soma: that site elicited the highest number of spikes, with latency decreasing with light intensity, characteristic of direct activation by light. Expressing red-sensitive opsins (ChRmine or ChrimsonR) allowed us to identify both classes of medium spiny neurons. We anticipate that Neuropixels Opto will become an essential tool for cell type-specific electrophysiology across the entire brain. We will thus continue this project with more rounds of design, fabrication, and thorough testing in vivo, aiming to minimize fabrication costs and functionality at multiple wavelengths, and to release a finalized probe in 2028 using the same non-profit distribution model as current Neuropixels probes.

Disclosures: A. Lakunina: None. **K.Z. Socha:** None. **A.J. Bowen:** None. **B. Karsh:** None. **M. Krumin:** None. **J. O'Callaghan:** None. **P. Neutens:** None. **H. Tilmans:** None. **B. Dutta:** None. **M. Häusser:** None. **N.A. Steinmetz:** None. **T. Harris:** None. **M. Carandini:** None. **K. Svoboda:** None. **J.H. Siegle:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Topic: I.04. Physiological Methods

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Title: Lightweight, reusable chronic implants for Neuropixels probes

Authors: C. BIMBARD[1], F. TAKÁCS[1], J. A. CATARINO[2], J. M. J. FABRE[1], S. GUPTA[3], M. D. MELIN[3], N. O'NEILL[1], M. ROBACHA[1], J. S. STREET[1], J. TEIXEIRA[2], E. H. VAN BEEST[1], A. M. ZHANG[4], A. K. CHURCHLAND[3], K. D. HARRIS[1], D. M. KULLMANN[1], G. LIGNANI[1], Z. F. MAINEN[2], N. L. ROCHEFORT[4], A. M. WIKENHEISER[3], M. CARANDINI[1], ***P. COEN**[1];
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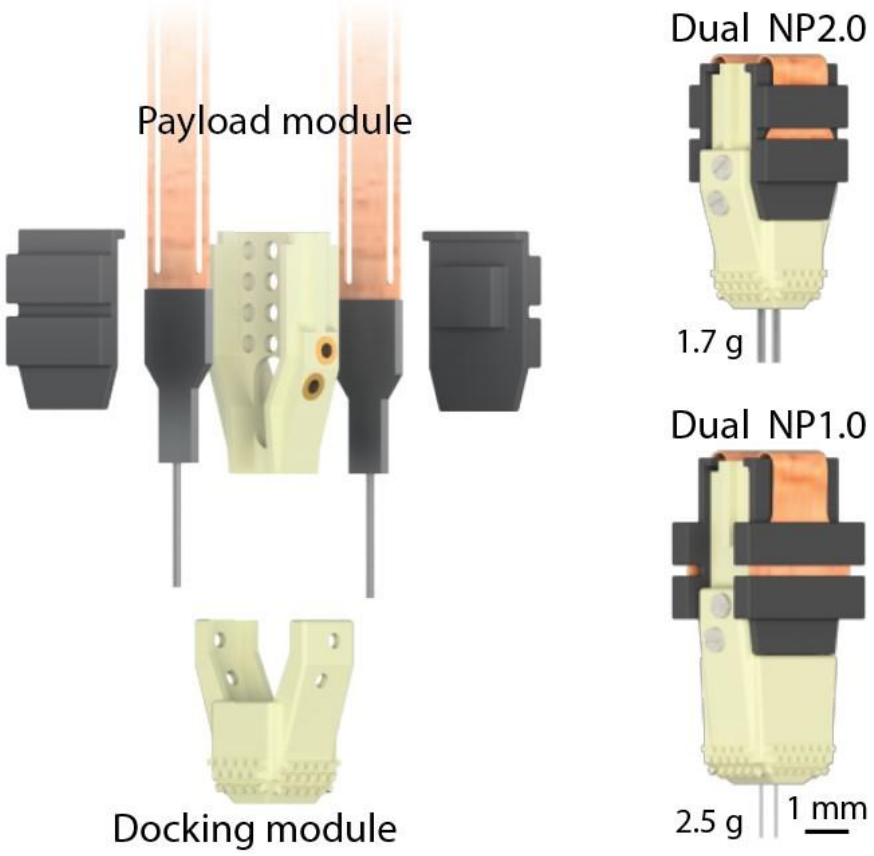

Abstract:

[Aims] Neuropixels probes have dramatically increased the number of neurons that can be acquired in a single experiment. With chronic recordings, these probes can track neurons across days and behaviors. There is thus substantial interest in developing chronic implants that are recoverable while being stable enough for prolonged recordings, and light enough for use in small animals such as mice.
[Methods] Here, we present the "Apollo implant", a two-module device for reversible chronic implantation of Neuropixels probes. The recoverable payload module (~$10) accommodates up to two Neuropixels probes, and the non-recoverable docking module (~$3) is cemented to the skull during implantation. The implant is 3D-printed using Formlabs Rigid Resin and weighs ~2.5 g with two 1.0 probes and ~1.7 g with two 2.0 probes. The design is open source and can be readily adjusted to change the angle of insertion, the distance between probes, or the implantation depth.
[Results] We successfully tested the Apollo implant in 5 laboratories, both in mice and in rats. The same Neuropixels probes were inserted up to 6 times with no significant change in recording quality. Recordings were stable across weeks and sometimes months, allowing neurons to be successfully tracked over days and for recordings to cover the entirety of 2.0 probes, while minimizing set-up time. The design has been independently printed, adjusted, and implanted across multiple labs. Successfully implanted subjects included freely moving mice and rats and head-fixed mice, with both 1.0 and 2.0 probes.
[Conclusions] The Apollo implant provides an open-access, flexible, inexpensive, lightweight,

and stable solution for chronic Neuropixels recordings which has been implemented across multiple labs, setups, and species.

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PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.19/WW5

Topic: I.04. Physiological Methods

Support: Marie Sklodowska-Curie Fellowship (101022757)
Wellcome Trust (223144)
EMBO (ALTF 740-2019)

Title: Fast and scalable method for tracking neurons across days in chronic recordings

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Abstract: [Intro] Chronic electrophysiological recordings with large-scale tools such as Neuropixels probes can record the activity of many neurons over months. However, it remains difficult to identify the same neurons across recordings. The standard method for large-scale recordings - to collate the recordings before running the spike sorting algorithm - becomes computationally intractable as the number of recordings increases. We developed a fast and scalable algorithm (UnitMatch) which uses spike waveforms to track neurons across independently spike-sorted recordings.
[Methods] UnitMatch is based on the average multi-channel waveform of every neuron. First, separate recording sessions are spike-sorted to extract multiple parameters for each neuron's waveform, including the average shape, location, and spatiotemporal trajectory. Second, we calculate a similarity score for each parameter for every pair of neurons across sessions. The sum of multiple similarity scores is used to provide potential matches and apply median drift correction. Finally, the similarity scores are weighted using a Naive Bayes classifier trained on the initial potential matches, yielding a posterior probability of match for each pair of neurons across recordings.
[Results] UnitMatch is reliable. Only 3.0±0.8% neurons were not matched with themselves between the first and second half of the same recording and 0.7±0.1% extra matches were made.

UnitMatch is fast, taking less than 5 minutes (tested for up to 28 Neuropixels recordings) on a standard desktop computer, regardless of recording duration. We tested the algorithm across multiple brain areas, and evaluated match quality using the functional responses of the neurons. For example, the distance between receptive field locations for neurons in the visual cortex was smaller for tracked neurons (20.3±40.9°) than for nearest neighbors (42.2±42.8°). Also, their autocorrelograms were more similar than those of neighboring neurons, and their correlations with the simultaneously-recorded population were stable.
[Conclusion] UnitMatch is a fast and reliable tool to investigate what aspects of the neural code are constant or change over recordings, e.g. due to learning.

Disclosures: **E.H. van Beest:** None. **C. Bimbard:** None. **J.M.J. Fabre:** None. **A. Lebedeva:** None. **F. Takács:** None. **M. Robacha:** None. **P. Coen:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.20/WW6

Topic: I.04. Physiological Methods

Support: NIH U19NS123716

Title: An optimized method for long-term, simultaneous multi-area Neuropixels recordings

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Abstract: Recent advances in high-density silicon electrode technology have facilitated large-scale, simultaneous neural measurements within many brain structures. Leveraging novel technologies to simultaneously insert many probes, neuroscientists can now record activity from hundreds to thousands of neurons in diverse brain regions. These developments have the potential to increase our understanding of how different brain areas work together to guide behavior. Nonetheless, these advances are mostly confined to head-fixed preparations, in which electrodes are introduced for recording and retracted at the end of the session. Many experiments require animals to be freely moving, and others, for instance longitudinal studies, require electrodes to remain implanted in the same location over many days. Overcoming these limitations poses significant challenges. The implant must be reusable, lightweight, and flexible enough for a variety of targeting approaches, while still maintaining stable recordings over many days.
To facilitate large-scale, parallel recordings in freely moving contexts, or across longer timescales, we introduce a flexible, lightweight method for chronic Neuropixels implantation and

recording. Using our novel implantation approach, we recorded simultaneous neural activity across 7 brain regions for up to 90 days using 3 Neuropixels 1.0 probes. The assembly weighs 1.2 grams, including a Neuropixels 1.0 probe (~0.6g with a 2.0 probe) and can be printed with a desktop 3D resin printer. This novel device allows for multiple probes to be independently implanted, and the optimization of the surgical protocol allows stable recordings with minimal artifacts due to brain motion even months after implantation. Surgical time is also reduced, thus enabling the implantation of multiple probes and quick recovery. Importantly, the probes can be retrieved in seconds without the need for stereotaxic devices or manipulators. We observed a drop in single unit yield over the initial 4 days, after which the recordings remain stable for months.
This new design and optimized surgical procedure can boost the number and stability of recorded units from many probes and is flexible enough to enable precise targeting of select brain areas. Further improvements to minimize immune response or improve long-term biocompatibility promise to help mitigate the initial drop in units.

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PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

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Topic: I.04. Physiological Methods

Support: Wellcome Trust (223144)
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Marie Sklodowska-Curie Fellowship (101022757)

Title: Stable brainwide structure of neural population activity across days

Authors: C. BIMBARD, E. VAN BEEST, J. FABRE, F. TAKACS, T. P. H. SIT, P. COEN, K. D. HARRIS, ***M. CARANDINI**;
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Abstract: [Introduction] Neural activity in sensory cortical areas is highly structured, and this structure is thought to reflect and constrain the computations performed by neural populations. For example, neurons in visual cortex differ in their correlations with the population activity (‘soloists vs choristers’, Okun et al., *Nature* 2015), and neurons in auditory cortex exhibit stereotyped sequences of activation (Luczak et al., *Neuron* 2009). Here we asked whether this structure is widespread across the brain or local to cortical sensory areas; and whether it changes over time, similarly to the ‘representational drift’ observed in some neuronal representations, or it is invariant across time.
[Methods] We tracked the activity of large populations of neurons in the awake mouse brain

across days, with chronic Neuropixels recordings using the "Apollo" implant (Bimbard et al SfN 2023) together with a new algorithm to match neurons across sessions ("UnitMatch", van Beest, Bimbard et al SfN 2023). Recordings were performed across cortical and subcortical regions including visual cortex, frontal cortex, superior colliculus and striatum. For each session, we then built a correlation matrix by measuring the total or spontaneous correlation of each neuron with every other neuron at different timescales, and we calculated the typical delay in firing between each pair of neurons.
[Results] The correlation matrices were highly stable across days (~0.8 correlation across matrices measured >20 days apart), especially when correlations were measured at fast timescales (<30 ms). A large part of the correlation structure could be explained by facial movements (~0.9 correlation between data and model), and this explainable part of the structure was stable across days. Moreover, the relative delay of spikes across neurons was also stable across days (~0.8 correlation >20 days apart). In the visual cortex, these delays were the same during spontaneous activity and in response to visual stimuli.
[Conclusions] We conclude that the structure of neuronal population activity in multiple regions across the mouse brain is highly stable across days. Both the strength of correlation and the relative timing of each pair of neuron's spikes were consistent across multiple days. This suggests constraints on the possible sequential activity patterns that a given cortical circuit may produce. Finally, changes in basic population structure may not explain representational drift, which may come from changes in other parts of the network.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.22/WW8

Topic: I.04. Physiological Methods

Support: 1R37NS128416

Title: Rejuvenation of silicon probes in acute electrophysiology

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Abstract: Multi-contact silicon probes are a popular and well-adapted technology for neurophysiology because they allow for simultaneous recordings of electrical activities from many neurons, greatly expanding the options for robust analysis of neural firing patterns. However, with repeated use in acute experiments, the probe's ability to isolate single units

degrades substantially, making them unusable typically after 3-5 experiments. This reduction in performance likely arises because repeated insertions into the brain removes the conductive polymer coating that is commonly employed to reduce the impedance of the electrodes. Here, we describe a method to re-coat these electrodes and then test whether the rejuvenated probes exhibit reduced impedance and improved ability to isolate single units. We tested 11 Cambridge Neurotech silicon probes (both linear and checkerboard varieties) during 86 recording sessions in 3 common marmoset monkeys. Each probe arrived out-of-the-box with an electrodeposited PEDOT-PSS (poly 3,4-ethylenedioxythiophene polystyrene sulfonate) coating on 64 gold 144 um^2 electrode contacts. The impedance of each electrode was recorded in sterile saline using an Intan RHD 2000 series chip using a 1000 Hz sine wave. This is the same system we used for acute neurophysiology recordings. In a typical experiment, we inserted the electrode through the dura, visual cortex, then tentorium, finally arriving in lobule VI or VII of the cerebellar vermis. In some sessions the recordings were also made from the deep cerebellar nuclei. A typical recording session lasted about 6 hours. Electrophysiological data were sorted using Kilosort 2.0 and Phy for curation. Exceptional care was taken to cleanly isolate each unit. With repeated use of the same probe, there was a marked increase in the mean and variance of the magnitude and phase of the impedance, and a corresponding decrease in the number of units. Once the signal quality had degraded beyond what was sufficient for recording, we cleaned the probe and removed the residual tissue that was attached by inserting it gently into a hard-boiled egg white. The egg white cleanly removed the tissue attached to the probe, as viewed through a microscope. We next recoated the probe in a solution of 10 mM EDOT monomer with 32 uM PSS using a current density of about $3mA/cm^2$ for 30 seconds. We iterated the recoating process until our impedance dropped to approximately 50 kOhms on a majority of the probe contacts. Recoating the electrode reduced the average impedance significantly and led to better recording quality upon subsequent uses. This technique proved to be a worthwhile endeavor and has greatly extended the life of our probes.

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Poster

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Program #/Poster #: PSTR117.23/WW9

Topic: I.04. Physiological Methods

Support: NIH Grant DC014044

Title: Assessing reliability of multisite silicon chronic arrays through accelerated soak testing and circuit modeling

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Abstract: Reliability of implantable microelectrodes has garnered much interest recently. Developing and certifying neural prosthetics, neuromodulation devices, and brain-machine interfaces typically requires *in vitro* accelerated tests to ensure optimal medical benefits with minimal risks. Microelectrodes are typically protected by layers of inert, electrically insulating materials, e.g., silicon dioxide/nitride or polymers. The onset of intra-channel leakage and inter-channel crosstalk may be indicative of insulation delamination and saline intrusion. Accelerated aging testing under a validated Arrhenius behavior is known to provide a reliable estimate of the device's lifetime *in vivo*. Previously we conducted multiple long-term chronic animal studies in the brain and spinal cord of the feline model using custom-designed multisite silicon-based microelectrode arrays. In this study, we fabricated and assembled the chronic devices with identical materials, incorporating a new feature: one shank containing exposed electrode sites and another completely insulated sites. This hybrid device configuration allows for testing of electrode-site specific properties and identifying failure in the insulation over a particular shank, wire-bonding, or other connection problems. We evaluated the total leakage development by measuring the access resistance R_A of the microelectrodes over time. Accelerated aging tests at soak temperatures of 39°C, 49°C, 59°C, and 75°C were conducted for up to 1.5 years. Results showed that R_A changed over time in both electrode cohorts with a temperature dependent rate of reaction. Most temperatures did not cause failure except at 75°C, where significant degradation occurred, likely due to the use of medical epoxy. To explain the observed R_A changes and putative mechanism of failure, we developed a simplified electrical circuit model. The model consists of a Howland current pump and a microstimulation-compatible Randles cell, in parallel with a 100kΩ calibration resistor and a leakage resistor R_L. We simulated this model using LTspice which enabled us to plot R_A as a function of R_L. This model-based plot of R_A vs. R_L closely resembled the experimental plot of R_A vs. soak durations in both covered sites and exposed sites at elevated soak temperatures. Thus, our circuit model allowed reducing the soak durations (time) to R_L since leakage paths develop over time (i.e., R_L decreases). These experiments and circuit model will serve as an important tool for evaluating the stability and condition of chronically implanted electrodes for microstimulation.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

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Topic: I.04. Physiological Methods

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.

Title: Strategies for improving the chronic in-vivo integration of SiNAPS neural probes and assessment of performances

Authors: A. PERNA[1], R. NOLS[1], G. ORBAN[1], C. STUBBENDORFF[1], M. VINCENZI[1], G. ANGOTZI[1,2], J. F. RIBEIRO[1], ***L. BERDONDINI**[1];
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Abstract: Intracortical neural probes constitute a key tool of modern neuroscience. Achieving chronic mechanical and electrophysiological recording stability is an important challenge in the field of neurotechnology. A common approach to improve the chronic stability of implantable devices is to reduce their sizes or to use flexible substrates. Both approaches, however, call for a trade-off on the number of recording sites, which ultimately impacts the information throughput and reliability of the recording. Active dense implantable neural probes based on CMOS technology, such as Neuropixel, Neuroseeker or, more recently, SiNAPS probes allow to overcome such limitation in the number of electrodes which can be integrated over shanks with small cross-sectional dimensions. Notably, while other CMOS neural probes integrate low noise neural amplifiers in the probe base, SiNAPS technology allows to reduce even further the number of connection lines in the shank by using in-pixel amplifiers and multiplexing circuits. However, it remains unclear how to assess the impact of the cross-sectional dimensions of such Si based CMOS devices on acute tissue damage during implantation. The mechanical damage that probes cause during their insertion constitutes a trigger for successive steps of foreign body reaction (FBR), which is currently one of the main limiting factors for achieving chronically stable intracortical neural interfaces. One potential strategy to study the impact of probe size and geometry on acute tissue damage and Blood Brain Barrier (BBB) disruption and to improve the integration of tissue penetrating high-density neural probes within brain tissue is to measure and potentially control the force required for their implantation. In fact, insertion force is expected to be correlated with the magnitude of iatrogenic injury induced and may constitute an objective metric to assess the extent of acute tissue damage. This strategy is foreseen to yield a more favorable postsurgical environment, reducing the extent of FBR in a chronic setting. We will present insertion force measurements and other strategies, acting both on probe design and on the implantation protocol, with the aim to advance the reliability of chronically implanted SiNAPS probes.

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Program #/Poster #: PSTR117.25/WW11

Topic: I.04. Physiological Methods

Title: Brain-wide, MRI-guided electrophysiology

Authors: *Y. BROWNING[1], G. F. LYNCH[2], S. TOTTEN[3], D. LEE[4], K. SVOBODA[2], J. H. SIEGLE[2];
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Abstract: Animal behaviors require coordinated neural activity across many interconnected brain regions. While high-density recording devices have now made it possible to record from a dozen or more brain regions at once, simultaneously recording connected nodes of a multi-regional neural circuit remains difficult. One challenge is that the interconnected portions of brain regions are often too small to reliably target using stereotactic coordinates. Each additional probe adds another opportunity to miss its target, reducing the probability of collecting a complete dataset.
Studies tracking the accuracy of stereotactic targeting based on skull landmarks estimate that electrode insertions have an average brain-surface offset of around 400 μm from their intended target (IBL et al., bioRxiv 2022; Narayanan et al 2022). To improve on these methods, we develop MRI-guided probe targeting in mice.
The goal of the method is to index a standardized brain coordinate system (CCF) to precision-machined fiducial points on a headframe with 100 um precision. The fiducial points, and by extension CCF locations, can then be harmonized with the laboratory coordinate system, allowing us to target specific atlas coordinates in that mouse.
We developed a stiff, MRI-compatible headframe that provides 10 μm-precise alignment in our recording apparatus (Groblewski et al., J. Neurosci. Methods 2020). After attaching the headframe to the skull, we collected 100 μm isotropic T1-weighted MRI volumes from mice using manganese-enhanced imaging (Massaad et al. 2010). The headframe included precisely machined fiducial holes that are filled with vaseline to be visible in MRI, allowing us to accurately align the MRI volumes to our recording apparatus. We then registered each mouse's MRI volume to the CCF. Prior to recording, we dipped all probes in DiI to facilitate histological reconstruction of probe tracks (Liu et al 2021). We assess our targeting accuracy by recordings from a retinotopically-defined region in the lateral geniculate nucleus (LGN), as well as by driving probes through additional anatomical landmarks that are clearly visible in both MRI and histology. We demonstrate that our MRI pipeline can improve targeting accuracy over conventional stereotaxic approaches, achieving 230 μm accuracy in early tests.
MRI-guided targeting of recording electrodes will increase both the success rate and repeatability of recordings from multiple interconnected brain regions in the mouse, which will in turn be crucial for understanding how multi-regional neural circuits generate cognition and behavior.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.26/WW12

Topic: I.04. Physiological Methods

Title: Mri localization of ultraflexible ultra-thin next-generation polymer electrodes

Authors: *E. ÖZIL[1,2], P. GOMBKOTO[1,2], T. B. YASAR[1,2], M. MARKS[3], A. VAVLADELLI[1], W. VON DER BEHRENS[1,2], M. F. YANIK[1,2];
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Abstract: It is important to localize the positions of chronically implanted ultrasoft polymer electrodes in vivo to identify the exact brain areas recorded and/or stimulated. However, localizing next-generation ultraflexible polymer electrodes by standard noninvasive imaging techniques such as magnetic resonance imaging (MR) or computed tomography (CT) has been impossible due to the material properties and microscale dimensions of these electrodes. We aimed at detecting our next-generation ultraflexible polymer multielectrode arrays with 2µm x 4µm individual electrode wire cross section. To increase electrode-tissue image contrast in standard anatomical MRI scans, we used 20nm diameter iron-oxide nanoparticles (IONP) which enhance both T2 and T2* contrast. A thin film of IONP was deposited in between two polyimide layers of individual electrode wire segments, where the pattern of IONP deposition and amount of IONP deposited was optimized to achieve specific MRI contrast patterns with high localization accuracy. Two 64-channel multielectrode arrays with and without IONP-deposition were implanted bilaterally through the dorsal hippocampus (dHPC) and thalamus in the rat brains (n=2). Our IONP-deposited electrodes were easily localizable (down to 68µm resolution) with a preclinical 7T MRI while the multielectrode arrays without IONP-deposition were invisible. We performed extracellular recordings from dHPC and thalamus bilaterally in freely moving rats. IONP-deposition did not impair the functional properties (e.g. impedance) of our electrodes, allowing excellent chronic recordings with high SNR. To validate the positions of electrodes found in MRI, we used electrophysiological landmarks (e.g. laminar amplitude profile of sharp-wave ripples) of the dHPC. The position of the IONP-deposited electrodes could be measured immediately after implantation and were tracked in the brain over several months. Our electrodes were also visible and easily localizable in clinical 3T MRI (300µm isovoxel) where we implanted them into a phantom. IONP-deposition allows faster scan times to localize the electrode array in the brain even under low SNR imaging conditions and at different MRI field strengths. Our approach can enhance the accurate interpretation of neural data in animal studies by precisely identifying anatomical coordinates of ultraflexible electrodes. In vivo localization capability can help to translate next-generation polymer electrodes into clinical usage. Knowing the positions of chronically implanted electrodes also enables chronic monitoring of the neighboring brain tissue for immune reactions/inflammation by noninvasive imaging.

Disclosures: **E. Özil:** None. **P. Gombkoto:** None. **T.B. Yasar:** None. **M. Marks:** None. **A. Vavladelli:** None. **W. von der Behrens:** None. **M.F. Yanik:** None.

Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.27/WW13

Topic: I.04. Physiological Methods

Support: NIH/NIBIB (P41-EB018783)
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McDonnell Center for Systems Neuroscience
Fondazione Neurone

Title: Vera: a user-friendly intracranial electrode localization interface

Authors: *J. R. SWIFT[1,2], M. ADAMEK[1,2,3], N. SYED[1,5,4], P. DEMAREST[1,4], P. BRUNNER[1,2,3];
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Abstract: Following intracranial electrode implantation, post-operative CT is coregistered to pre-operative MRI to identify electrode coordinates in MRI space. Knowledge of electrode positions relative to anatomical structures is critical for clinical planning and neuroscientific research. While there is no standard electrode localization method, current approaches to the problem have tedious workflows, often requiring institutional knowledge and having limited utility. A flexible tool for localizing electrodes could improve speed and accuracy while providing a data standard. Here we present an intuitive Versatile Electrode Localization Framework (VERA) integrating external tools into modular workflows that can easily be customized to meet users' unique needs. VERA is implemented as a centralized MATLAB GUI through which users may use native and external tools, such as SPM12 or FreeSurfer. To test if VERA improves electrode localization accuracy, precision, and speed, 5 naïve users completed manual and VERA-assisted localization tasks in one electrocorticography (ECoG) and one stereo-EEG (SEEG) patient. Coordinates from an experienced user's manual localization were used as ground truth electrode locations (n = 110 SEEG, 67 ECoG). Left-tailed Wilcoxon rank sum tests were used to compare the median errors and durations of assisted and manual trial conditions. Levene's test was used to compare the standard deviations (STDs) of error. Using VERA improved SEEG electrode localization accuracy (median number of points ± STD = 107

± 21 manual, 109 ± 3 assisted; median error = 0.48 mm manual, 0.41 mm assisted; $p < 0.01$), precision (STD = 0.52 mm manual, 0.25 mm assisted; Levene's $p < 0.01$), and speed (median time ± STD = 60 ± 21 min manual, 49 ± 20 min assisted, $p < 0.05$). VERA also improved ECoG electrode localization accuracy (median number of points ± STD = 67 ± 4 manual, 67 ± 0 assisted; median error = 0.82 mm manual, 0.45 mm assisted; $p < 0.01$), precision (STD = 1.17 mm manual, 0.45 mm assisted; Levene's $p < 0.01$), and speed (median time ± STD = 59 ± 21 min manual, 11 ± 4 min assisted, $p < 0.05$). These results demonstrate a clear improvement in electrode localization performance when assisted by VERA compared to manual localization. This study demonstrates that VERA significantly improves intracranial electrode localization performance for both SEEG and ECoG electrodes. Limitations of this study include the small number of participants and that those participants only performed localization for a single SEEG and ECoG patient. We recommend further validation testing with more participants and trials of each type.

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Poster

PSTR117. Electrophysiology Techniques: Methods for Recording from Many Single Cells in Parallel

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR117.28/WW14

Topic: I.04. Physiological Methods

Support: UH3- NS100553
UG3-NS130202
R01-NS119520

Title: A method for stimulus transient removal by leveraging the absolute refractory period: Validation with cathodic versus anodic deep brain stimulation

Authors: *J. BLOCK[1,2], M. AWAD[3], J. OLSON[3], R. SMITH[3], J. N. BENTLEY[3], M. HOLLAND[3], S. A. BRINKERHOFF[3], A. NAKHMANI[3], M. MOFFITT[1,2], H. WALKER[3]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Boston Scientific, Valencia, CA; [3]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Neurostimulation generates large electrical artifacts that obscure underlying physiological potentials. Stimulus-evoked recordings are typically "blanked" for 1 to 2.5 ms after pulse onset to remove artifact and enable visualization of the signal after the "blanking" window, but physiological signals present during the "blanking" are unfortunately also subtracted with this technique. We have proposed an alternative method for separating artifact from neural response based on templates and the refractory properties of neurons, and that we hypothesize reveals valuable neural activity within 1 ms of the pulse onset. In the present work, we use the

difference in stimulation properties of anodes and cathodes to generate supporting evidence of the effectiveness of our novel artifact removal technique. We studied intracranial electrophysiology in 5 consecutive patients with Parkinson's disease undergoing deep brain stimulation (DBS) surgery as part of routine care. Pairs of monopolar cathodic and anodic stimuli were delivered from the DBS electrode across a range of inter-stimulus intervals (0.3 to 16 ms) and recorded from unused adjacent DBS electrodes. Broadband sampling (100 kHz) and precise synchronization yielded robust event-related potential templates for the stimulus transient during the absolute refractory period. We then subtracted this template waveform across experimental conditions and analyzed the residual signals. These potentials display absolute and relative refractory periods and phase-independence from the stimulus transient. The earliest detectable responses are almost entirely obscured by stimulus artifact and occur at very short latencies with a peak, on average, at 0.27 ms after pulse onset (range of 0.19 to 0.38 ms). Monopolar cathodic and anodic DBS pulses elicit distinct patterns of local tissue activation. In 5 out of 5 of the subjects, cathodic stimuli elicit larger local tissue responses than anodic stimuli at the same amplitude, consistent with known clinical phenomenology (i.e., lower activation thresholds with cathodic stimulation). The early tissue response for cathodic stimulation was, on average, 3.3 times greater than for anodic stimulation (range of 1.3 to 7.2 times larger). This method for stimulus artifact removal improves on prior efforts because it allows direct measurement of local tissue responses without requirements for stimulus polarity reversal (each of which can engage distinct neural elements), template scaling, specialized filters, or other techniques. Future neuromodulation systems could utilize this method or its extensions as a proxy for dose or circuit engagement.

Disclosures: **J. Block:** A. Employment/Salary (full or part-time):; Boston Scientific. **M. Awad:** None. **J. Olson:** None. **R. Smith:** None. **J.N. Bentley:** None. **M. Holland:** None. **S.A. Brinkerhoff:** None. **A. Nakhmani:** None. **M. Moffitt:** A. Employment/Salary (full or part-time):; Boston Scientific. **H. Walker:** F. Consulting Fees (e.g., advisory boards); Varian.

Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.01/WW15

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

Support: NHMRC Grant APP1188414

Title: SENSE - an automated computational nerve model development pipeline for neural engineering

Authors: Y. XIE[1], P. QIN[1], T. GUO[1], A. ABED[1], S. DOKOS[1], N. LOVELL[1], ***D. TSAI**[2]; [1]UNSW, SYDNEY, Australia; [2]BIOMEDICAL ENGINEERING; ELECTRICAL ENGINEERING, Univ. of New South Wales, Randwick, Australia

Abstract: A variety of implantable electrodes, ranging from the relatively non-invasive cuff electrodes to the penetrating intrafascicular multichannel electrodes (TIME), have been developed for nerve stimulation and recording, to improve neural interfacing performance. Computational models are commonly used to aid the design of these electrodes. Due to the large number (≥ 10s of thousands) of fibers within a nerve and the complex tissue structure (e.g. myelination, vasculature, fat), it is desirable for the simulation platform to be computationally efficient yet capable of capturing the complex, heterogeneous tissue structure, especially in the contexts of extracellular stimulation. We began by implementing a flexible and scalable Python / MATLAB-based toolkit, SENSE (Scalable Electrobionic Nerve Simulation Environment), for automatically creating models of nerve stimulation in the hybrid NEURON / COMSOL ecosystem, to take advantage of NEURON's efficient cable-equation-based simulations and COMSOL's finite-element-based representation of the non-homogeneous tissue space.
We then built using our toolkit a rat sciatic nerve model containing 14 fascicles with 1,170 myelinated (A-type, 30%) and unmyelinated (C-type, 70%) fibers to study fiber responses over a variety of TIME arrangements (monopolar and hexapolar) and stimulation waveforms (kilohertz stimulation and cathodic ramp modulation). Our population-based simulations suggested that kilohertz stimuli provide selective activation of targeted C fibers near the stimulating electrodes but also tended to activate non-targeted A fibers further away. However, C fiber selectivity can be enhanced by hexapolar TIME arrangements that confined the spatial extent of electrical stimuli.
Demonstrating the generalizability of our toolkit, we also developed a human vagus nerve model with 309 myelinated A-fibers (Aα-type 0.6%, Aβ-type 5.5%, Aδ;-type 93.9%), 231 myelinated B-fibers, and 460 unmyelinated C-fibers. Importantly, the model incorporates fat tissue and blood vessels. Efforts are ongoing to optimize stimulation waveforms to preferentially activate B-fibers (for seizure suppression and visceral modulation) while blocking Aδ;-fibers (avoiding painful sensations, blood pressure variations and initiating bradycardia).

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Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.02/WW16

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

Support: NIH Grant 1R01NS118606-01

Title: Simulating the decision to initiate, maintain and sequence a feeding sequence in Aplysia

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Abstract: *Aplysia* feeding behaviors are characterized by repeated cycles of radula protraction followed by retraction. The decision to initiate a sequence and to protract is made by neurons B63 and B31/B32. Initiation and maintenance of retraction is made by activating a plateau potential in neuron B64. Before the system decides to protract, B63 fires, gradually depolarizing B31/B32, until the depolarization initiates a plateau potential in B31/B32, thereby producing protraction. Because B63 and B31/B32 are electrically coupled, maintained depolarization of B31/B32 depolarizes B63, which fires while B31/B32 remains depolarized. B63 also depolarizes B31/B32 via a slow, voltage-dependent cholinergic synapse. The B31/B32 plateau potential is unusual, in that it is not endogenous, but rather is synaptically driven. Thus, B63 excites B31/B32 via both fast and slow synapses from B63 to B31/B32, and via electrical coupling. What are the functions of these multiple connections in producing the B31/B32 plateau potential? To determine the relative contribution of these 3 components to the initiation and maintenance of the plateau potential, we simulated B63 and B31/B32 and their connections. The B31/B32 simulation utilized data on inward and outward currents derived from voltage clamping. We found that initiation and maintenance of the B31/B32 plateau potential required all 3 components that connect B63 to B31/B32.
We then tested the possibility that one of the components contributing to B31/B32 plateau potential might separately have another function. In particular, we examined whether the slow, voltage-dependent EPSP might function in a slow, sub-threshold depolarization of B64 that eventually initiates its plateau potential. The B64 plateau potential terminates the B31/B32 plateau potential, thereby stopping protraction, and initiating retraction, the next phase of the behavior. It is important to note that in spite of much effort, a neuron that excites B64 to initiate its plateau potential has not been found. Adding B64 to the simulated circuit with properties partially derived from voltage clamp experiments, and exciting B64 with only the slow, voltage dependent synapse from B63, successfully activated the plateau potential of B64 after a delay, shutting off the B31/B32 plateau potential and the first phase of feeding, and initiating the next phase of behavior. These simulations translate features of a behavior to biophysical features of cells and synapses, shedding light on how the decision to initiate a behavior is made, and how successive phases of a behavior may be sequenced.

Disclosures: I. Hurwitz: None. **A. Raphael:** None. **A.J. Susswein:** None.

Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.03/WW33

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

Title: Simulation of dendritic plateau potentials in striatal spiny neurons

Authors: *S. MITRA[1], S. ANTIC[2], W. LYTTON[3];
[1]SUNY Downstate Med. Ctr., New York, NY; [2]UConn Hlth., Farmington, CT; [3]DHSU, Brooklyn, NY

Abstract: We performed computer simulations of striatal spiny neurons (SPNs) using physiologically plausible multi-compartment cell models to explore the generation of plateaus in SPN dendrites using NEURON simulation software. D1R and D2R SPN's used the same channel distributions though they had different morphologies, with D1R cells having greater arborization of the dendritic tree. Our simulations showed that NMDA-generated dendritic plateau potentials could occur in dendrites with spread to the soma. Plateaus occurred in both D1R and D2R SPN's. Fast sodium and potassium channels with small time constants were reciprocally distributed along dendrites. High speed sodium channels were preferentially concentrated near the soma and were distributed with decreasing density going from proximal to distal along dendrites, with the opposite for potassium channels. Low threshold calcium channels were distributed preferentially in distal dendrites. Glutamatergic stimulation was provided in a section of a dendrite with NMDA and AMPA receptors present in synaptic locations, with NMDA receptors distributed in extrasynaptic sites, to model for glutamate spillovers. Glutamatergic pulses were provided with gradually increasing intensity; with higher intensity stimulation leading to dendritic plateaus with spread to other dendrites and soma. The D1R SPN had wider plateaus compared to D2R SPN plateaus. In D1R SPN, high intensity stimulation produced sustained plateaus that did not terminate abruptly and instead gradually terminated over seconds. In D2R plateaus terminated for all intensities. Plateaus in D1R SPN's had a maximum amplitude of -20 mV at the stimulation site with an average width of 300 ms with recording performed at the site of stimulation, while D2R SPN had a maximum amplitude of -13 mV and an average width of 300ms at the same stimulation intensity. The plateaus showed an initial sodium spike, followed by a brief rise and decay. The decay from the peak was faster in D2R cells compared to D1R cells. The plateaus were dependent on the distribution of sodium, calcium and potassium channels. Identification of the mechanisms and roles of plateaus in SPNs may assist in development of new therapeutic approaches to Parkinson's disease.

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Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.04/WW34

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

Support: DFG grant SFB1080

Title: A dynamic, data-driven computational model of the GluA2-containing AMPA receptor distribution in dendrites and synapses under basal and plasticity conditions

Authors: *S. WAGLE[1,2], N. KRAYNYUKOVA[1,2], M. K. KRACHT[3], A.-S. HAFNER[4,5], A. ACKER-PALMER[3,6], E. M. SCHUMAN[5], T. TCHUMATCHENKO[2,1];
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Abstract: AMPA receptors (AMPARs) are ionotropic glutamate receptors, usually localized in the postsynaptic compartment, that mediate fast synaptic transmission and are regulated by synaptic plasticity. The number of AMPARs at a synapse is often used as a proxy for synaptic strength. At individual synapses, AMPAR copy number is modulated by altering the diffusion of the receptors along the plasma membrane and/or by adjusting the endocytosis/exocytosis frequency [1,2]. Moreover, active molecular motor-based transport is necessary to deliver the subunits of the AMPARs to distal synapses [3]. Recent molecular and imaging techniques provide a glance into this extraordinarily complex trafficking of receptors in dendrites and spines. However, the role of individual trafficking mechanisms in determining the availability of AMPARs and the spatial and temporal scales of their copy number change for hetero-synapses after long-term potentiation (LTP) induction remains poorly understood. To address this, we combine computational modeling with experiments to describe the long-range, steady-state distribution of the GluA2-containing AMPARs on the surface and in the cytoplasm. We performed fluorescent labeling of antibodies against endogenous GluA2-containing AMPARs in the same neuron [4]. We used different fluorophores before and after permeabilizing the neuronal membrane to separate the surface and intracellular population. We analyzed this dataset to calculate the balance between GluA2 endo/exocytosis rates under basal conditions. We fitted our model to the normalized fluorescence intensity in 100 µm long dendritic stretches to estimate the global-transport parameters at steady-state. Finally, we compute the synaptic enrichment of GluA2 as the fluorescence intensity ratio from the spine to the shaft. Overall, we have built a data-driven modeling framework describing the endogenous distribution of GluA2-containing AMPAR globally and locally. Next, we will predict heterosynaptic plasticity's temporal and spatial extent after LTP induction derived from our model by modulating AMPAR trafficking kinetics. **References:** [1] Anggono & Huganir 2012, *Curr. Opin. Neurobiol.* **22**, 461-469;[2] Patterson et al., 2010, PNAS, 107 (36) 15951-15956; [3] Hangen et al .2018, *Cell Reports* **24**, 1001-1012.e3; [4] Bissen et al., 2021, Cell Reports 34, 108923;

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Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.05/WW35

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

Title: En masse generation of biophysical single-neuron modelsbased on multimodal cellular data sets of human cortical inhibitory cell types

Authors: *Y.-T. WU[1,2,3], J. MOORE[3], C. A. ANASTASSIOU[2,4,5];
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Abstract: The past decade has seen an unprecedented accumulation of data at the single-cell level giving rise to unique, multimodal sets of gene expression patterns, morphologies, and electrophysiology characteristics. This high-resolution census of neuronal types in the brain constitutes an essential step towards a mechanistic understanding of circuits and brain computations. However, linking cellular identity and activity to circuits and neurophysiological signals remains daunting. The goal of this work is to causally link between the various modalities describing a single-neuron or cell type and to do that at scale. For example, how does the expression of individual ion channels or certain morphological features of a cell shape affect its electrophysiology features and vice versa? To address this question, we develop computational workflows to generate bio-realistic single-neuron computational models of individual human neocortical neurons linking transcription, morphology, and physiology. Next, we use these models to probe cause-and-effect and establish how the various modalities map to each other. Here, we present a collection of biophysically realistic models for human inhibitory cells, including subtypes of parvalbumin-, somatostatin-, vasoactive intestinal peptide-, lysosomal associated membrane protein 5-expressing interneurons. Our starting point is a data set with 73 neurons assayed with Patch-seq including their reconstructed morphologies. We develop a single-cell multi-objective optimization (MOO) workflow and constrain it appropriately for human multimodal data sets [Nandi et al. 2022]. The MOO procedure progressively evaluates 200 (generations) x 4096 (populations) models comparing model vs. experiment electrophysiology features for the same intracellular input and keeps the best 40 performing models (so-called “hall of fame” or HOF models) for each experiment/cell. With 73 experimental cells (25 PV, 8 SST, 21 VIP, 19 LAMP5) and 40 HOF model for each cell, a total of 2,920 models were created. Next, we attempt to associate specific expression patterns with electrophysiology features for each cell type. We find that several conductances co-vary with a subset of ion channel genes across cell types. To causally link between specific ion channels and electrophysiology features we then perform variance-based (Sobol) sensitivity analysis . The computational models, tools and resources will ultimately allow testing mechanistic hypotheses about the role of different mechanisms and neuronal types in neural circuit function.

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Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.06/WW36

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

Support: NIH-NIDCD R01 DC012347

Title: Uncovering the mechanisms of ephaptic transmission at the vestibular hair cell-calyx synapse: What computational modeling has taught us

Authors: A. GOVINDARAJU[1], A. LYSAKOWSKI[3], R. EATOCK[4], ***R. RAPHAEL**[2]; [1]Applied Physics/Bioengineering, [2]Rice Univ., Houston, TX; [3]Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [4]Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Quantal transmission is accepted to be the dominant mode of neurotransmission in the nervous system. However, increasing attention is being paid to mechanisms of neuronal signaling that do not involve neurotransmitters. These mechanisms have traditionally been grouped as "ephaptic". Ephaptic mechanisms have been controversial in neuroscience - in part because they have not been understood at the biophysical level. Some synapses in the nervous system exhibit extended synaptic architectures. One example is the vestibular hair cell-calyx (VHCC) synapse, which exhibits a form of neurotransmission referred to as non-quantal transmission. Experiments have demonstrated fast and slow modes of this transmission. We have constructed a biophysical model of the VHCC synapse that explains existing experimental results. To simulate transmission between hair cell and afferent neuron, our VHCC model uses 1) Hodgkin-Huxley-style ion currents based on whole-cell recordings, 2) continuity equations to describe changes in electric potential within hair cell, cleft, afferent calyx and fiber, and 3) electro-diffusion equations for K^+ and Na^+ in the synaptic cleft. The extent of ephaptic coupling depends on ion channel expression in the pre-synaptic and post-synaptic membranes as well as the geometry of the synapse (Govindaraju et al, PNAS 2023). The synapse exhibits both capacitive and resistive coupling, with fast transmission attributed to the rise in potential in the synaptic cleft, and slow transmission attributed to the rise in $[K^+]$. Our original model considered a situation that assumed continuity of $[K^+]$ with an extracellular fluid bath - i.e., an isolated hair cell. We now consider the influence of additional constraints on diffusion in narrow extracellular spaces that more faithfully reflect native tissue architecture. Model results predict that diffusion constraints can enhance ephaptic transmission, depending on the ion-clearing capacity of surrounding cells. Our modeling approach, while specific for the VHCC synapse, can be adopted to explain ephaptic mechanisms observed in other areas of the nervous system.

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Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.07/WW37

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

Support: NRF-2021R1A3B1077481
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NRF-2022R1I1A1A01072579
P0011266

Title: Recreating the Human Brain Choroid Plexus Structure and Dynamics in a Microfluidic Chip for Neuropathology Research

Authors: *J. LIM[1], S. RHEE[2], H. CHOI[2], J. LEE[2], N. JEON[2];
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Abstract: The human brain choroid plexus (ChP) plays a crucial role as the primary source of cerebrospinal fluid (CSF) and maintains the blood-CSF barrier (BCSFB). The ChP's unique structure and dynamic CSF flow have important implications for brain physiology and pathophysiology, including the metastasis of tumors to the central nervous system. However, current preclinical models fail to accurately recapitulate the complex architecture, CSF dynamics, and immune microenvironment of the human ChP, hindering therapeutic development. In this study, we developed a human ChP-on-a-chip model that incorporates the recreated architecture of the ChP and physiologically relevant CSF dynamics. The platform utilizes open microfluidic patterning and an engineered extracellular matrix (ECM) with laminin to construct a multilayered ChP vascular network and epithelial layer. Additionally, we employed image processing and analysis techniques to mimic the pulsatile CSF flow within the system and incorporated a laminin-containing hydrogel to replicate the brain's extracellular matrix (ECM). The human ChP-on-a-chip model exhibited a downregulation of tight junction expression led by the introduction of dynamic CSF flow, consistent with ChP capillaries. Epithelial cells lining the vasculature demonstrated ciliogenesis, increased cellular coverage area, and enhanced tight junction expression in response to recapitulated CSF flow. Enzymatic analysis confirmed that the composition of CSF in the platform matched previous findings. Furthermore, to validate the model's utility for drug screening, we reconstructed a tumor microenvironment (TME) by introducing HER2-overexpressing cancer cells (SKBR3 cells) and macrophages. Under dynamic flow, HER2 overexpression was maintained in the cancer cells, and the anti-cancer effect of an intrathecal anti-HER2 therapy was enhanced compared to static conditions. The presence of macrophages in the TME under dynamic flow upregulated their motility and significantly reduced their cytotoxic effects on cancer cells. The development of our human ChP-on-a-chip provides a valuable tool for studying ChP pathophysiology and advancing our understanding of neurodegenerative diseases and cancer metastasis. By enabling the investigation of the ChP's complex structure and dynamics, this platform holds promise for the development of targeted therapeutics to treat cancers that have spread to the ChP. Ultimately, our work contributes to bridging the gap between in vitro and in vivo models, facilitating more comprehensive research in the field of neuroscience.

Disclosures: **J. Lim:** None. **S. Rhee:** None. **H. Choi:** None. **J. Lee:** None. **N. Jeon:** None.

Poster

PSTR118. Cellular Models

Location: WCC Halls A-C

Time: Sunday, November 12, 2023, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR118.08/WW38

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

Title: The effects of neuron morphology and spatial distribution on the selectivity of DRG stimulation

Authors: *J. FAROOQUI[1,2], A. C. NANIVADEKAR[3], M. CAPOGROSSO[4], S. F. LEMPKA[6], L. FISHER[5];
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Abstract: Epineural electrical stimulation of the dorsal root ganglion (DRG) is a clinically approved therapy for managing refractory pain and a promising approach for sensory neuroprostheses. Our lab has shown that epineural DRG stimulation with macroelectrodes selectively activates neural targets similarly to stimulation with penetrating microelectrodes. To develop targeted DRG stimulation for focal sensory feedback, we must understand the mechanisms of selective activation. Therefore, we used computational models to characterize the mechanisms of neural selectivity during DRG stimulation via epineural and penetrating electrodes, focusing on the impact of realistic neuron morphology and spatial distribution on neural recruitment by each electrode type.
We developed three DRG models consisting of finite element method (FEM) models populated with equivalent circuit neuron models of either axons or pseudounipolar neurons (consisting of somas, axon initial segments, stem axons, T-junctions, and peripheral and central axons). DRG models are differentiated by type and configuration of neurons: (1) *axon-only*: axon models placed randomly (2) *random*: pseudounipolar neuron models placed randomly, and (3) *realistic*: pseudounipolar neuron models placed according to realistic spatial distributions. The FEM models represent neural tissue, epineurium, epineural space, bone, and implanted penetrating and epineural electrodes, and are used to calculate extracellular potentials resulting from current injection. All models include Aα and Aβ afferent types drawn from realistic fiber size distributions.
Our models indicate that the unique neuron geometry and spatial distribution of a real DRG constrain neural recruitment. Specifically, epineural stimulation preferentially recruits the initial segment of the stem axon (adjacent to the cell body) in the realistic configuration, while epineural stimulation of other configurations and penetrating stimulation of all configurations preferentially recruit t-junctions and axons. This suggests that both neuron morphology (pseudounipolar structure) and spatial distribution (densely packed axons near the DRG center and less densely packed cell bodies near the DRG circumference) drive selectivity of epineural and penetrating electrodes. Epineural stimulation boasts a wider dynamic range than penetrating stimulation, enabling the selective recruitment of small numbers of additional neurons as stimulation amplitude is increased.
Our results suggest that the anatomical features of the DRG make epineural stimulation an effective method for delivering focal sensory feedback.

Disclosures: J. Farooqui: None. **A.C. Nanivadekar:** None. **M. Capogrosso:** None. **S.F. Lempka:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

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Poster

PSTR118. Cellular Models

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Program #/Poster #: PSTR118.09/WW39

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

Support: NIMHNIBIB 1R01EB026939
NIH-NINDS 1R01NS130759
Oak Ridge Institute for Scientific Education

Title: The effects of temperature and pressure on voltage activated channels

Authors: J. MILLER[1], B. PAHLAVAN[1], ***F. SANTAMARIA**[2];
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Abstract: Just as any other protein, voltage gated channels are subjected to the laws of thermodynamics. We have used Macro Molecular Rate Theory to describe how the reaction rates of voltage activated channels change with temperature. We demonstrated that the historically, and widely used, Q_{10}-factor results in accumulated errors, calling into question how biophysical models of neurons are parametrized. Here we present a generalization of this theory by including the effects of pressure. Based on fits to experimental results we derive values for heat capacity, enthalpy and entropy of the activation barrier for sodium, potassium, and calcium conductances. The pressure analysis allowed us to calculate volume expansivity and compressibility of sodium and potassium channels. We conclude that high pressures can stabilize rate at lower values. We also propose a physical explanation for the activation volume using channel structure and gating processes. Our combined theoretical effort provides a unified thermodynamical framework to study the effects of temperature and pressure on single cells and networks.

Disclosures: J. Miller: None. **B. Pahlavan:** None. **F. Santamaria:** None.

Poster

PSTR118. Cellular Models

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

Support: National Institute of Deafness and Other Communication Disorders of the National Institutes of Health under award number R01DC019278

Title: Neuron-type Identification using Spatiotemporal Features of Extracellular Recordings

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Abstract: Traditionally, researchers have used features of extracellularly-recorded action potentials (EAP) such as trough half-width or trough-to-peak duration to identify putative excitatory and inhibitory single unit activity in cortex. Machine learning models trained on additional features such as repolarization slope provide moderate improvements beyond binary classifications (Trainito et al, 2019). In addition, studies suggest that EAP features may vary in predictable ways based on recording location relative to the morphology of the recorded neuron (Gold et al, 2006). In this study, we simulated extracellular recordings from linear probes for over 100 biophysically-detailed, multicompartmental neuron models, systematically varying the recording location. Using an unsupervised machine learning approach, simulated data were used to extract spatial and temporal features of EAP data that predict underlying neuron-types with links to morphological structures. These results provide a hierarchy of distinct morphological-electrophysiological groups of neuron-types that can be used to classify EAP recordings, which we apply to recordings from primary auditory cortex of marmoset. We also use simulations to demonstrate how spatial and temporal patterns of synaptic inputs affect these classifications. In particular, we demonstrate how these patterns contribute to the shape of different phases of EAP waveforms.

Disclosures: K. Doxey: None. **V. Haynes:** None. **Y. Zhou:** None. **S.M. Crook:** None.

Poster

PSTR118. Cellular Models

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Program #/Poster #: PSTR118.11/WW41

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

Support: NIH Grant EY033975
NIH Grant MH099045

Title: Pynebranch: a platform for biophysical modeling of in vivo-like dynamics in single neurons.

Authors: *T. M. MORSE[1], M. J. HIGLEY[2];
[1]Yale Univ. Sch. Med., New Haven, CT; [2]Neurobio., Yale Sch. of Med., New Haven, CT

Abstract: Single neurons generate spike output through an interplay of synaptic inputs and intrinsic excitability. However, a cortical pyramidal neuron (PN) may receive several thousand excitatory and inhibitory synaptic inputs per second, and the functional organizing principles that allow the generation of normal output are not well understood. Here, we developed a novel computational platform using the software package Neuron and a Python-based user interface for biophysically realistic modeling of synaptic integration and membrane voltage dynamics in single morphologically reconstructed neurons (PyNeBranch). Published morphologies of layer 2/3 PN dendritic arbors were obtained (NeuroMorpho.org, ModelDB.science) and converted into Neuron-compatible multi-compartmental models at a regular spacing of 1 micron. Up to two dendritic spines were attached at each dendritic shaft compartment, and each spine and shaft compartment could receive an excitatory and inhibitory synaptic input. Specific spine and synaptic densities are adjustable across the cell, with initial models matched to published values. Synaptic inputs included AMPA- and NMDA-type glutamate and A-type GABA conductances matching experimental data. A variety of sodium, potassium, and calcium channels were incorporated using a novel parametric framework to define channel gating properties. Whole-cell brain slice recordings of sub- and supra-threshold activity were used as targets to optimize channel properties using the BluePyOpt algorithm (HH NEURON builder and local cluster installation). We then used published in vivo recordings from cortical PNs and GABAergic interneurons to set the mean activity for each model synapse. Initial results using independent Poisson-distributed inputs showed that single neurons are sensitive to the balance of excitatory and inhibitory drive, with a E:I ratio of ~0.9 required to produce physiological spike output. Moreover, spatiotemporal correlations of inputs along the dendrites strongly influenced synaptic integration and spike generation. Overall, our work demonstrates a powerful new approach for linking network dynamics to single cell biophysics and highlights the importance of dendritic integrative properties for circuit function.

Disclosures: T.M. Morse: None. **M.J. Higley:** None.

Poster

PSTR118. Cellular Models

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

Support: HHMI Gilliam Fellowship Grant GT13547-2020

Title: Optimization of fully differentiable ODE neurons using the backpropagation of error algorithm

Authors: *I. S. JONES[1], K. P. KORDING[2];
[1]Neurosci., [2]Neurosci. and Bioengineering, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Neuroscientists fit simulations of single neurons to data by varying neuron model parameters. Fitting morphologically and biophysically detailed versions of these neuron models is a computationally expensive high-dimensional optimization problem. Due to this limitation, neuroscientists judiciously apply dimensionality reducing abstractions to their models in order to investigate specific questions. These abstractions bias neuroscientists toward simple conceptions of neurons, leaving behind questions that consider the complexity of dendritic excitability and computation. To address this limitation, we develop a way to use the backpropagation of error algorithm, routinely used on high-dimensional neural network models, on a fully differentiable neuron model by using Neural ODE solvers. We employ GPUs to efficiently simulate many morphologically detailed neurons in parallel and effectively fit heterogeneously distributed ion channel densities. We find that accurate approximation of ground truth parameters can be augmented using dendritic current input instead of somatic current input alone. This method removes the dimensionality limitation on neuron models by supplying an alternative optimization method that is appropriate for high-dimensional models. Differentiable neuron models will allow for further detailed work on dendritic simulation.

Disclosures: I.S. Jones: None. **K.P. Kording:** None.

Poster

PSTR118. Cellular Models

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Program #/Poster #: PSTR118.13/WW43

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

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Biophysically detailed cortical neuron models with genetically defined ion channels

Authors: *D. MANDGE[1], Y. ROUSSEL[1], S. VAN DORP[1,2], T. DAMART[1], A. T. JAQUIER[1], H. MARKRAM[1,2], D. KELLER[1], R. RANJAN[1,2], W. VAN GEIT[1];
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Abstract: Neocortical neurons can be classified into different electrical firing types (e-types). Traditionally, biophysically detailed electrical models (e-models) for these neurons have been constructed using generic ion channel models including transient and persistent sodium channels, potassium channels, as well as high- and low-voltage activated calcium channels. We now have access to 47 genetically defined ion channel models corresponding to various potassium, sodium, calcium, and hyperpolarization-activated cyclic nucleotide-gated ion channels (HCN). These

genetic ion channel models were based on experimental data from the heterologous expression of the corresponding genes. We constructed cortical e-type models using detailed morphological reconstructions and electrophysiological data from the rat somatosensory cortex using these genetic channels along with some generic channels. We used Python software packages such as eFEL and BluePyEfe to extract electrical features from the electrophysiological data and BluePyOpt to optimize the parameters of our e-models. These e-models can reproduce firing properties as observed in in vitro recordings. Electrical features of the e-models were found to be within 3-5 standard deviations of the corresponding mean experimental recordings. These biophysically detailed models can enable a better understanding of electrical activity in normal and pathological states of neurons.

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Poster

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

Support: EU Grant Agreement No. 945539 (Human Brain Project SGA3)
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Title: Building hippocampal neuron models by collecting online resources via the Hippocampus Hub

Authors: *L. BOLOGNA[1], A. TOCCO[1], R. SMIRIGLIA[1], A. ROMANI[2], F. SCHUERMANN[3], M. MIGLIORE[4];
[1]CNR, Palermo, Italy; [3]Campus Biotech, [2]EPFL - Blue Brain Project, Geneva, Switzerland; [4]Natl. Res. Council, Palermo, Italy

Abstract: Data-driven neural modeling is increasingly being adopted as a standard approach for building biophysically detailed models of brain cells, circuits, and regions. Also, the possibility to easily access existing neural models is becoming fundamental for computational neuroscientists, as the scientific community grows wider, and models increase in types and number. Nonetheless, data and models are rarely reused since it is difficult to retrieve, extract and/or understand relevant information and, even when accessibility is guaranteed, scientists are often constrained to manual download and modification of individual files, neural data analysis, and model optimization and running. To alleviate these problems, we created a dedicated section in the Hippocampus Hub portal, an online scientific hub for research on the hippocampus (https://www.hippocampushub.eu/), that gathers data and components for the construction of hippocampal biophysically and morphologically accurate cell models, from different sources (i.e., internal, https://neuromorpho.org/, https://senselab.med.yale.edu/ModelDB/). Through a simple click-and-collect procedure, similar to filling the shopping cart of an online store, researchers can intuitively select reconstructed morphologies, electrophysiological traces and NEURON .mod files (describing the biophysical mechanisms of neural cells in the NEURON simulation environment), in order to build a neuron model of interest. Successively, the constructed model is optimized against the chosen experimental data, run and finally saved in the EBRAINS Model Catalog repository (https://model-catalog.brainsimulation.eu/), via the EBRAINS Hodgkin-Huxley Neuron Builder (https://hbp-bsp-hhnb.cineca.it/hh-neuron-builder/), that lifts the burden of software installation and use off the users, through an intuitive and user-friendly web interface.

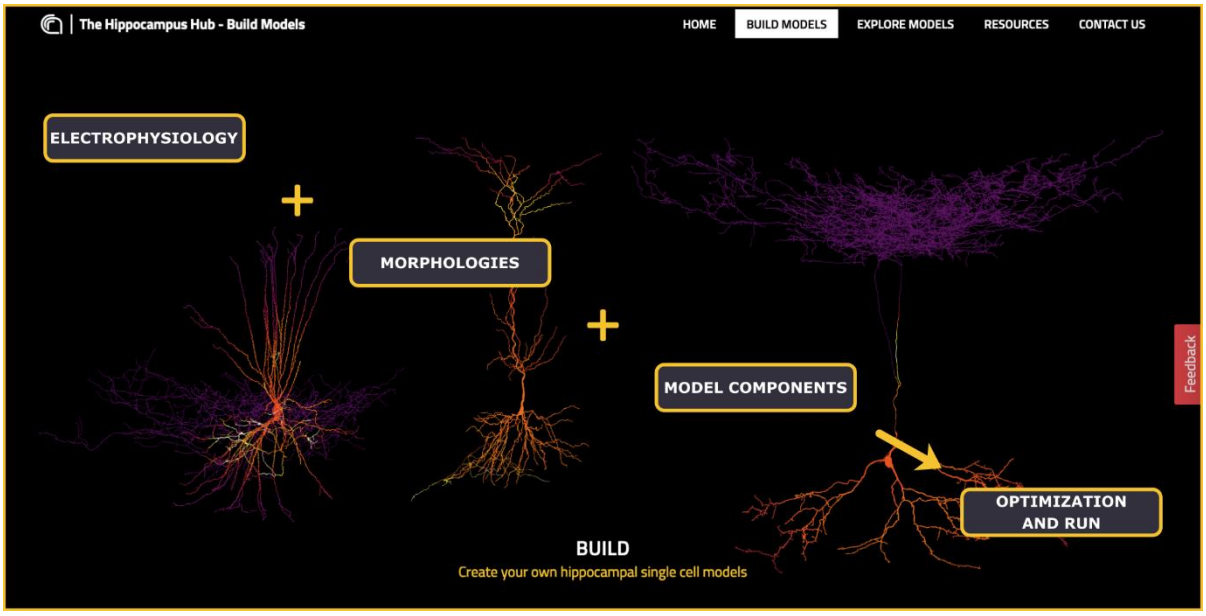

Figure 1.The Hippocampus Hub Build section landing page (background);the components collection and model optimization workflow (foreground).

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Poster

PSTR118. Cellular Models

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Program #/Poster #: PSTR118.15/WW45

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

Support: NIH MH122023
NSF OAC-1730655

Title: Model reduction techniques for biophysical neurons

Authors: *D. R. FAGUE[1], V. OMELYUSIK[2], S. S. NAIR[1];
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Abstract: Diverse single cell model formulations have been proposed in the past to investigate the integrative properties of neurons. However, recent findings related to various dendritic spikes (e.g., Na+, NMDA+ and Ca2+ spikes) have dramatically changed our perception of the role of dendrites in neuronal function, a topic that is beginning to increasingly interest researchers. These findings have, in parallel, resulted in the development of morphologically realistic neuronal models with hundreds of compartments and tens of thousands of synapses. Here we compare the performance of proposed reduced order model formulations on cortical pyramidal neurons of L5 and L2/3 layers to morphologically realistic models as far as reproducing neurocomputational and integrative properties including gain modulation and extracellular potential recordings. In each case, we start with morphologically detailed single neuron model from the literature or from a database. Model reduction techniques include adapting an existing efficient method neuron_reduce (Amsalem et al.) to add morphological realism to the tuft dendrites as well as a few other reduction features. Information about known dendritic spikes in different dendritic locations as well as about in vivo properties is used to constrain the active conductances along all dendrites. The first example case is of an L5 pyramidal model (Hay et al.) developed using the NEURON simulation environment that provided good match with biological data. For comparison we start with in vitro (resting membrane potential, membrane time constant, input resistance), and current injection (F-I curve) features. We then added features such as known spatial location of Na, NMDA and Ca2+ spikes (with naturalistic drives), mediation of somatic bursts through differing distributions of excitatory inputs and the activation of tuft calcium spikes as reported in a recent full scale L5 single cell model, as well as match with in vivo extracellular potential recordings. The second example case considered is the L2/3 cell type. An important objective is the quantification of performance tradeoffs for all the neurocomputational and integrative properties.

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Poster

PSTR118. Cellular Models

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Program #/Poster #: PSTR118.16/WW46

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

Title: Mathematical model for TRPM8 dynamics in cold sensory neurons

Authors: *E. M. DUDEBOUT[1], W. D. VAN HORN[2,3], S. M. CROOK[4];
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Abstract: Transient receptor potential melastatin 8 (TRPM8) is a polymodal, nonselective, calcium-permeable ion channel primarily responsible for cold thermo-transduction within mammalian cold sensory neurons (CSNs). TRPM8 activation depends on numerous stimuli including membrane potential, calcium concentration, temperature, and chemical ligands such as menthol. CSNs, a subset of the somatosensory system, encode cold temperature via electrochemical firing patterns and are dependent on TRPM8 for successful cold signal transduction. During cooling, CSNs exhibit bursting behavior, clustering action potentials with prolonged periods between subsequent bursts. In contrast, during heating, CSNs undergo a cessation of firing, displaying a hysteresis event seen in temperature ramp experimental data. These properties constitute CSNs' dynamic response to temperature, allowing them to differentiate stimuli and interpret resting temperature. Mathematical models provide valuable insight into biochemical phenomena such as these firing patterns and the underlying mechanisms which are difficult to analyze experimentally. Prior models have been unable to replicate CSNs' dynamic response to temperature while maintaining a physiologically accurate representation of all TRPM8's gating dependencies. In this study, we create a gating model for TRPM8, capable of replicating experimentally recorded channel kinetics with menthol activation. Our model includes kinetics based on a temperature-dependent TRPM8 model proposed by Olivares et al. (2015). We include a menthol-dependent voltage shift of activation, constrained by voltage-clamp data from TRPM8 transfected HEK293 cells with the application of menthol. After optimization using a genetic algorithm, our gating model successfully replicates the channel kinetics and conductance for HEK293 dynamic temperature ramp data. Moreover, we have integrated this gating model into a conductance-based CSN model to replicate complex, dynamic firing patterns. We use the whole-cell CSN model to predict interactions between the activators of TRPM8 gating and their effects on overall firing patterns.

Disclosures: E.M. Dudebout: None. **W.D. Van Horn:** None. **S.M. Crook:** None.

Poster

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Program #/Poster #: PSTR118.17/WW47

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

Support: NIH Grant R35 NS097185

Title: Experimental determination of the phase resetting curve for optimal prediction of input-output responses in oscillating neurons.

Authors: *E. OLIVARES[1], J. A. JONES[2], J. PENA[3], C. J. WILSON[4];
[1]UTSA-College of Sci., San Antonio, TX; [2]Univ. of Texas at San Antonio, San Antonio, TX, United States, San Antonio, TX; [3]Univ. of Texas at San Antonio, Univ. of Texas at San Antonio, San Antonio, TX; [4]Univ. Texas San Antonio, Univ. Texas San Antonio, San Antonio, TX

Abstract: The infinitesimal phase resetting curve (iPRC) characterizes a neuron's oscillatory responses to external inputs across the inter-spike interval (ISI). Ideally, the iPRC should predict the response to any stimulus waveform, and any broad-bandwidth stimulation should provide the information necessary to extract an iPRC. However, there is not a general method for retrieving the iPRC from experimental data. Theoretical iPRC solutions assume infinitesimally small stimulus amplitudes, but for any empirical estimations, the stimulus amplitude must be large enough to counteract the neurons' inherent variability. On the other hand, there is an upper limit to the stimulus amplitudes for which the iPRC can be empirically estimated. In this study, we employed an assumption-free evolutionary algorithm (EA) method to extract the iPRC, which optimizes phase model predictions of external globus pallidus (GPe) neuron spike-time responses to noise barrages. The EA iPRCs aligned with those measured using two established methods (multi-linear regression and weighted spike triggered average), with all three methods demonstrating robustness and producing similar iPRCs, even when assessed using large-amplitude noise current pulses. Increasing the amplitude of noise pulses led to an increase in noise-induced ISI variability beyond the neurons' intrinsic variability and resulted in iPRCs with improved input-output prediction. These three methods were then utilized to estimate the iPRCs from spike-time responses to sinusoidal current waveforms. However, only the EA method proved to be robust in this stimulus protocol. iPRCs estimated by the EA based on the spiking responses to sine waves were similar to iPRCs determined by the EA based on spiking responses of the same neuron to noise barrage stimuli. Finally, iPRCs estimated from the spiking responses to noise using any of the methods accurately predicted the spiking responses to sine wave stimuli. These results suggest that a single iPRC can provide accurate predictions of spike timing responses to a broad array of stimuli, and that the EA can ascertain the iPRC from spike responses to a wide range of stimuli.

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